984

Department of Health
and Human Services

Abstracts of Small Business Innovation Research (SBIR) Phase I and Phase II Projects

Fiscal Year 1984

HE 20.3047:

READEX FICHE best copy available

Department of Health
and Human Services

NEWARK PUBLIC LIBRARY

DEC 17 1985

U. S. GOVT. PUBS.
DEPOSITORY 376

Abstracts of Small Business Innovation Research (SBIR) Phase I and Phase II Projects

Fiscal Year 1984

TABLE OF CONTENTS

PREFACE

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging 1
National Institute of Allergy and Infectious Diseases 8
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases 28
National Cancer Institute 47
National Institute of Child Health and Human Development 103
National Institute of Dental Research 116
National Institute of Environmental Health Sciences 121
National Eye Institute 129
National Institute of General Medical Sciences 136
National Heart, Lung, and Blood Institute 156
National Institute of Neurological and Communicative Disorders and Stroke 198
Division of Research Resources 211
National Library of Medicine 223

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

National Institute on Alcohol Abuse and Alcoholism 224
National Institute on Drug Abuse 227
National Institute of Mental Health 230

CENTERS FOR DISEASE CONTROL

National Institute for Occupational Safety and Health 236

FOOD AND DRUG ADMINISTRATION

Center for Food Safety and Applied Nutrition 238

HEALTH RESOURCES AND SERVICES ADMINISTRATION 239

OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

National Center for Health Services Research 240

Office of Adolescent Pregnancy Programs 241

HEALTH CARE FINANCING ADMINISTRATION 242

OFFICE OF HUMAN DEVELOPMENT SERVICES 246

SOCIAL SECURITY ADMINISTRATION and the
OFFICE OF THE ASSISTANT SECRETARY FOR PLANNING
AND EVALUATION 257

INDEX--AWARDEE ORGANIZATIONS 259

INDEX--STATE/AWARDEE ORGANIZATION 264

PREFACE

Public Law 97-219, the Small Business Innovation Development Act of 1982, was passed by Congress and signed by the President in order to increase the role of small businesses in federally supported research and development. This legislation created the Small Business Innovation Research (SBIR) Program, involving 12 federal agencies, of which the Department of Health and Human Services (DHHS) is the second largest participant. Within the Department, the National Institutes of Health (NIH) accounts for 92% of the SBIR activity.

The SBIR Program, as mandated by P.L. 97-219, consists of three phases, the first of which is intended for technical feasibility studies. Phase I awards are generally $50,000 for a period of approximately six months. Phase II, considered the principal research and development phase, is to continue the research effort initiated in Phase I. Awards for Phase II are made for periods of 1-3 years for amounts normally not to exceed $500,000. Only Phase I recipients are eligible to seek Phase II support. In Phase III, the small business is to pursue, with private capital, the commercialization of the results of the research funded in Phases I and II.

In FY 84, the second year of the SBIR Program, the DHHS made 282 SBIR awards, 226 of which were for Phase I research and 56 of which were for the support of Phase II activities. These awards amounted to approximately $23,300,000, exceeding by $760,000 the set-aside mandated by the legislation. The Phase I grants that were funded were selected from 912 applications and the Phase II awards were selected from 96 proposed projects. Of the total sum awarded by DHHS in FY 84, $20.9 million was funded by NIH, the lead agency within the Public Health Service for implementation of the SBIR Program.

Awards are made on the basis of scientific and technical merit, with consideration given also to program relevance, potential for commercial applications and availability of funds.

The abstracts in this publication are organized by funding agency within DHHS, and by awarding component within each agency (where appropriate). The abstracts for Phase I projects are followed by abstracts for Phase II, whenever a component has made both types of awards. Names, addresses, and telephone numbers of the awardee organizations are provided for those who may wish to contact these companies for additional information.

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Phase I Projects

Title of Project:	Age Differences in Word Processing
Principal Investigator:	Penelope K. Elias
Awardee Organization:	Beech Hill Enterprises, Inc. Box 229 Mount Desert, Maine 04660
Telephone Number:	(207) 244-3931

An expanding telecommunications technology now makes it possible to perform typesetting operations at home using a relatively inexpensive home computer as an input terminal. This offers an opportunity for older persons, particularly those who lack transportation or physical mobility, to be gainfully employed at home as typesetters or word processors in other business-related contexts.

However, current training materials for word processing are oriented toward younger, computer-literate adults rather than older adults. Older adults may not be able to work as word processors unless training materials for middle-aged and older adults are developed. Such training materials require data on the unique problems and assets that older persons have with typesetting. Unfortunately, systematic data do not exist.

The Phase I effort will evaluate age-related differences in ability to use current instructional materials and to learn word processing. Difficulties with instructional materials will be related to difficulties with certain input and editing operations in word processing, particularly those with typesetting applications.

In Phase II, this information will be used to construct age-valid instructional materials that will be evaluated for comprehension and performance. The commercial availability of these materials should enhance productivity in private industry and government, while providing older persons with an equal opportunity to participate in an important new industry.

Title of Project:	A Computer Managed Interview Service for the Elderly
Principal Investigator:	John R. Tole
Awardee Organization:	Digital Analysis Corporation Post Office Box 2850 Reston, Virginia 22090
Telephone Number:	(703) 471-0396

A computerized data base will be developed to manage an interview service for clients of agencies offering services to the elderly. Caseworkers, prompted by the data base, will periodically phone clients to check their health and social status and to relay timely health information.

The resulting product will be a computer program and a procedure for its use that should allow more efficient delivery of services to the aged as well as a means for collecting long-term health-related statistics in this population.

During Phase I, an existing data base system will be modified to prompt the interviews and appropriately maintain the collected data. In collaboration with the staff of a university hospital geriatric service, the suitability/acceptability of the system and the specific questions to be used will be examined in a group of outpatients followed by that service.

In Phase II, the system resulting from the first phase will be tested by two agencies providing services to the elderly, one located in a city in Massachusetts and the other in rural Virginia. A comparison will be made between this system and existing methods of evaluating the health and well-being of the clients of these agencies.

Title of Project:	Exercise Feedback: Motivation Value in Older Exercisers
Principal Investigator:	Richard G. Schweikhardt
Awardee Organization:	Fitness Information Technology 4227 Northeast 94th Seattle, Washington 98115
Telephone Number:	(206) 524-7293

The increasing number of older people in the United States means that in 15 years, up to 50 million Americans will be over 65 and in need of safe, attractive, cost-effective exercise programs. Practically no systematic investigations have been conducted into the role that information systems can play in improving such exercise programs.

This program aims to demonstrate the key role that information feedback can play in motivating older people to engage in effective, long-term exercise programs and showing how an exercise information system can contribute to exercise program cost reductions and safety.

During Phase I, a prototype exercise information system is being constructed, installed in a facility environment, and functionally tested. This prototype system is based on a comprehensive exercise information system, to be built during Phase II, that can be used in both a facility and a home environment.

To mitigate the physical deterioration that occurs during aging, people must be motivated to participate in effective, long-term exercise programs. Without innovations in exercise methods and technology, many older people will be excluded from the most effective programs by high cost, safety uncertainties, and lack of motivation.

Title of Project:	**Device for Automatic Detection of Urination**
Principal Investigator:	**Otakar Jonas**
Awardee Organization:	**Jonas, Inc.** **1113 Faun Road** **Wilmington, Delaware 19803**
Telephone Number:	**(302) 478-1375**

The objectives of this project are to develop an inexpensive disposable undergarment device for early automatic detection of urination and to design a quantitative device for use in clinical research and other applications. The electronic output of the detector system will trigger a signal observed by the person wearing the garment and/or by others (for example, a nurse). The device will be useful as a research tool, clinical monitor, and personal health care item. It will be of particular benefit to the elderly who have skin problems.

During Phase I, undergarment materials (shields, absorbents, barriers) suitable for use with the urination detection system are being selected and evaluated, and the detector and electronic signal transmitter-receiver are being designed. Several prototypes of the undergarment detection system and two prototypes of the transmitter-receiver will be built and laboratory tested. After this step is successful, the device for quantitative measurement of the volume of urine will be redesigned, with the prototype to be built in Phase II. Both devices should be evaluated on patients in Phase II, when the types of output signals to best fit various needs of medical research and clinical, nursing, and personal care will be selected.

Title of Project:	Drug Management System
Principal Investigator:	Frank C. Wroga, Jr.
Awardee Organization:	Migatron Corporation 1601 North 31st Avenue Melrose Park, Illinois 60160
Telephone Number:	(312) 343-1122

A feasibility study of a system for assisting geriatric patients in managing multiple prescription and over-the-counter drugs is being conducted. While the system is directed primarily toward the geriatric patient, it can be employed by any drug user.

The drug management system consists of two devices, a patient-prompting device (alarm watch) and a special medication container capable of organizing a multiple drug regimen. The prompting device will consist of a battery-powered watch (either wrist or pocket) with multiple programmable alarms. The watch will be programmed to give audible, visual, and/or tactile alarms whenever the patient is to take a drug. The special medication container, filled by the pharmacist, will dispense (or indicate) the drugs that are to be taken at those times. The two devices will be small enough and light enough to be easily carried all day by the patient.

Title of Project:	Applications of Information Technology for the Elderly
Principal Investigator:	Stuart R. Schwartz
Awardee Organization:	Senior Software, Inc. 2202 Fillmore Street San Francisco, California 94115
Telephone Number:	(415) 563-5315

This research addresses the role that personal computers can play in broadening the elderly's range of experience with information technology and in enhancing their psychological well-being. Successful completion of the project will produce: (1) specific, marketable computer software tailored to the needs of the elderly, (2) a combined package of computer software and hardware enhancements that will meet the requirements of older adults, (3) advanced understanding of the influence of appropriate computer applications on psychological well-being and social interaction among the elderly, and (4) knowledge of how to introduce computers and telecommunications to the elderly, so that this technology can be used for recreational, educational, and health maintenance purposes.

To accomplish these objectives, the research employs an experimental design using two senior centers as field locations. Personal computers will be introduced at the centers, using both existing game software and early versions of new software produced specifically for this project. The impact of computer use on senior center participants will be assessed in comparison to the effects of alternative interventions. A final segment of the research will be a market survey to identify target markets for the research products.

Title of Project:	**Fall Prevention System for the Aged**
Principal Investigator:	**David P. Colvin**
Awardee Organization:	**Triangle Research and Development Corporation** **Post Office Box 12696** **Research Triangle Park, North Carolina 27709**
Telephone Number:	**(919) 467-2878**

This project involves designing and developing a mobile system to prevent a dangerous fall by an aged or handicapped individual. Such a development could extend and complement nursing home staff use, reduce medical costs due to injuries, improve patients' locomotion and exercise, and promote their sense of independence and confidence. The design of the system may one day permit its extension into the home as well as into hospitals and other chronic care centers.

This effort is built upon knowledge gained over the past 5 years from the development of a passive mobile restraint system for a local nursing home. In that system, a patient can be tethered to a mobile reel attached to a monorail on the ceiling, and the reel can apply a variable braking force to prevent a fall. This new effort will develop an active mobile restraining system, which should have greater capability and application. Such a system will use microelectronics to position the restraining reel for support while walking and for control during falls.

Phase II Project

Title of Project:	High Resolution Tactile Aid for Deaf/Blind and Deaf
Principal Investigator:	Frank A. Saunders
Awardee Organization:	Tacticon Corporation 151 Third Street San Rafael, California 94901
Telephone Number:	(415) 456-3512

This project continues the research, development, and evaluation associated with a wearable, high-resolution, microprocessor-based tactile sensory aid for the deaf and deaf/blind.

Objectives include the completion of six prototype units suitable for field testing at collaborating centers serving the deaf.

Under Phase I, speech discrimination studies were conducted, showing that a 16-channel aid, with appropriately designed acoustic characteristics, could be effective in communicating essential speech features, in improving the accuracy of lipreading, in promoting auditory environmental awareness, and in facilitating speech therapy.

A follow-on funding commitment has been obtained from a non-Federal source, and additional capital will be provided if the field tests of the proposed prototypes are positive.

This research is part of an ongoing program to develop a commercially feasible speech communication and training aid for profoundly deaf persons who cannot understand speech through conventional amplification hearing aids. If successful, this approach will provide a nonsurgical alternative to persons for whom cochlear implant prostheses are not appropriate.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Phase I Projects

Title of Project:	PreReduced Anaerobically Sterilized (PRAS) Antibiotic Susceptibility Testing for Anaerobes
Principal Investigator:	Marion E. Cox
Awardee Organization:	Anaerobe Systems 3074-A Scott Boulevard Santa Clara, California 95050
Telephone Number:	(408) 727-1309

The purpose of this project is to design a product for anaerobic susceptibility testing that has the following features: (1) the ability to determine minimal inhibitory concentrations of antibiotics for anaerobic bacteria, (2) the ability to grow extreme oxygen-sensitive organisms, (3) simplicity, and (4) easily interpretable results.

The mortality rate of anaerobic infections can be very high if the infectious agent is not identified and the proper therapy initiated. Before the mid-1970's, identification of the infecting anaerobe was sufficient for proper treatment; however, with increased use of newer antibiotics, the antibiotic resistance of several groups of commonly encountered pathogenic anaerobes has increased. The antibiotic resistances observed are not limited to specific groups of organisms nor are they limited to particular antibiotics. Therefore, susceptibility testing of anaerobic bacteria isolated from clinical material now is necessary and should be performed routinely.

The procedure recommended by the National Committee on Clinical Laboratory Standards (NCCLS) for testing antibiotic susceptibilities of anaerobic bacteria is extremely cumbersome and also has growth problems with individual strains of oxygen-sensitive organisms. Similarly, the commercial systems currently available for antimicrobial susceptibilities give inconsistent results and are incapable of supporting the growth of the more oxygen-sensitive and nutritionally fastidious organisms. The results from these systems tend to give lower values or false susceptibilities for certain antibiotics and organisms.

During Phase I investigators will design a process by which production and packaging of test antibiotic susceptibility panels will be done under strict anaerobic conditions. Also, various nutritional supplements will be tested to determine if their addition to the NCCLS-recommended medium will improve growth of certain nutritionally fastidious anaerobes, especially anaerobic cocci. The completed product will be compared to the NCCLS-recommended procedure.

Title of Project: Rapid Detection of Cytomegalovirus Antigen in Urine

Principal Investigator: Douglas J. McAllister

Awardee Organization: Atlantic Antibodies
10 Nonesuch Road, Post Office Box 60
Scarborough, Maine 04074

Telephone Number: (207) 883-4154

Cytomegalovirus (CMV) appears to be an ubiquitous viral pathogen. It is a highly opportunistic agent and a member of the Herpes family of viruses. Due to its latency, it can recur abruptly, erupting as a lethal infection. The spectrum of the morbidity and mortality caused by CMV includes congenital, perinatal, postnatal, organ transplant, and transfusion infections. Current diagnosis is not well standardized, and is based on the appearance of cytopathic effect in a suitable host tissue culture. Time for diagnosis is long (7-21 days) and specificity is poor.

This research project is designed to develop an enzyme immunoassay to rapidly detect CMV antigen in urine. During Phase I development of monoclonal antibodies to various polypeptides of the CMV virion is taking place. In Phase II, the monoclonal antibodies will be fully characterized and then used (1) as tools to purify CMV polypeptides for use as immunogens in the production of polyclonal monospecific antisera, and (2) as potential diagnostic reagents in conjunction with the polyclonal reagents to develop a sensitive (polyclonal), specific (monoclonal), rapid assay to detect CMV shed in the urine of infected individuals. It is anticipated that sensitivity will have to be greatly increased over that of conventional colorimetric enzyme-linked immunosorbent assays (ELISA), and this will be approached in several novel ways by examining other enzymes, fluorogenic substrates, and alternate solid phases.

Potential commercial applications of such an assay are great, as this need is not currently being met. Such an assay could be expected to be widely used in pediatric wards, prenatal clinics, oncology chemotherapy settings, transplantation clinics, and transfusion centers.

Title of Project:	**Control of Schistosomiasis by Rotifer Emissions**
Principal Investigator:	**Margaret A. Stirewalt**
Awardee Organization:	**BRinc** **12111 Parklawn Drive** **Rockville, Maryland 20852**
Telephone Number:	**(301) 881-3300**

Schistosomiasis, caused by parasitic flatworms living in the mesenteric/vesical veins, is the second most important infectious disease of humans. Producing chronic illness, it spreads in developing countries who have increasing demands for water and intensified irrigation. It is a major contributor to the high level of morbidity and mortality in endemic areas.

Molluscicíding, sanitary engineering, and chemotherapy have not been able to keep the disease in check. Additional control measures are needed. One such approach involves biological interference with disease transmission in the field. To some extent interference with transmission occurs naturally: by predation of cercariae, miracidia, and snails by certain fish, prawns, annelids, turbellaria, and carnivorous plants.

A new approach to reducing transmission depends on immobilization of cercariae, the larva that infects man by penetrating intact skin. In the laboratory a water-soluble factor emitted by a symbiotic rotifer species colonizing vector snails does this by paralyzing the cercariae, thus reducing their capacity to emerge from snails and then to infect man.

Phase I objectives are to: (1) fractionate this anticercarial rotifer factor in water from cloned cultures of rotifer; (2) isolate and purify the active fraction(s); and (3) characterize and define it chemically and structurally.

Title of Project:	**Treatment of Herpes Infections with Platinum Complexes**
Principal Investigator:	**Robert C. Taylor**
Awardee Organization:	**Delta Metals, Inc.** **Post Office Box 851** **Rochester, Michigan 48063**
Telephone Number:	**(313) 377-2333**

Herpes simplex virus, especially types one and two (HSV-1 and HSV-2), is one of the most feared diseases in the world today. No known cure is available for the treatment of this disease. Commercial drugs provide only temporary relief. Based on anecdotal evidence and preliminary tissue culture studies, certain platinum complexes show considerable promise as effective therapeutic agents for herpetic infections. This research project will test 10 platinum complexes in a combination of in vitro and in vivo studies. One of these, cisplatin, will be investigated extensively to bring it to the stage of clinical testing by the end of Phase I. Six other platinum complexes, all known antitumor compounds, will be investigated in vitro against various strains of HSV-1 and HSV-2. The remaining three complexes, newly synthesized in this laboratory and containing the cis-$Pt(NH_3)^{2+}$ moiety bound to three known antiviral drugs (acyclovir, ara-ADA, and cyclaradine[2]), will be characterized and in vitro testing will be initiated. Phase II will involve (1) extensive clinical evaluation of cisplatin with the aim of commercial application, (2) completion of the in vitro and in vivo studies of the remaining nine complexes, and (3) the onset of clinical trials for the most promising antivirals in this group.

Title of Project:	**Diagnosis of Bacterial Infections**
Principal Investigator:	**Huey-Lang Yang**
Awardee Organization:	**Enzo Biochem, Inc.** **325 Hudson Street** **New York, New York 10013**
Telephone Number:	**(212) 741-3838**

A method to develop a model system for nonradioactive DNA hybridization/detection for identification of bacteria will be developed. DNA for ampicillin resistance (amp^r) will be labeled with biotinylated deoxyuridine triphosphate by nick translation and will be used as a probe. Colony hybridization procedures for the detection of amp^r in Escherichia coli (E. coli) will then be developed. Detection of hybridized biotinylated DNA will be done by detection of biotin by streptavidin, a biotin-binding protein linked to a color-producing enzyme.

Once the system is established, attempts will be made to detect sequences of lower copy number and of shorter length. Attempts will be made to shorten the time required to perform the procedure.

This model system is being developed as a basis for adaptation to direct (nongrowth) tests for bacterial pathogen-containing clinical samples. Potential commercial significance that could be realized from development of this technology is the fast and convenient diagnosis and characterization of bacterial infections.

Title of Project:	Production of Composite Monoclonal Immunoglobulins
Principal Investigator:	Kirk E. Fry
Awardee Organization:	Gene Labs, Inc. 1055 Lemon Street Menlo Park, California 94025
Telephone Number:	(415) 329-0310

Murine monoclonal antibodies are not useful for repeated administration to man because of the number of foreign antigen determinants they contain. Production of human monoclonal antibodies would be desirable for a variety of approaches in prophylaxis and therapy of disease, and also for protection against contact with noxious agents. The investigators are developing a procedure that will permit rapid isolation of composite human monoclonal antibodies in which preselected mouse variable regions have been substituted for the human variable regions conveying any desired specificity to the human antibody. The procedures involve a minimum of in vitro DNA reconstruction work or clone screening and therefore would be applicable for production of a wide variety of antibodies. Potential applications include pretreatment of individuals exposed to infectious or toxic agents and rapid protection against the spread of infections.

Title of Project:	New Approaches to Production of HLA Typing Reagents
Principal Investigator:	Kirk E. Fry
Awardee Organization:	Gene Labs, Inc. 1055 Lemon Street Menlo Park, California 94025
Telephone Number:	(415) 329-0310

Human class II histocompatibility antigen typing is already of substantial importance in determining disease susceptibility in individuals. Present serologic methods of class II antigen typing are limited by the polyclonal nature of many antisera, by the fact that many of the available human antisera react with multiple different determinants, and by the difficulty of obtaining allele-specific as compared with species-specific murine monoclonal antisera against human DR class II MHC antigens. Investigators are developing a procedure that will rapidly make it possible to clone and express composite class II antigens that have single exons from human DC, DR, or SB antigens incorporating and substituting for corresponding exons of analogous mouse antigens. These will then be used for immunization procedures to generate mouse monoclonal antibodies, a much larger fraction of which will be allele specific rather than species specific. Therefore, these procedures could lead to the efficient production of a new generation of serologic reagents for human MHC typing that would provide much better resolution than the currently available reagents.

Title of Project:	Monoclonal Antibodies and Immunoassay for cAMP and cGMP
Principal Investigator:	Harvey J. Brandwein
Awardee Organization:	Genetic Diagnostics Corporation 160 Community Drive Great Neck, New York 11021
Telephone Number:	(516) 487-4719

The cyclic nucleotides, cAMP and cGMP, are important regulatory molecules that are now recognized as mediators in a vast number of normal and pathological processes. Such insights have increased the need for generally available technology that will allow the convenient and accurate measurement of the cyclic nucleotides in research and clinical settings. The investigators are pursuing the generation of murine monoclonal anti cAMP/cGMP antibodies and fluorescent enzyme immunoassay systems for the rapid and sensitive measurement of the cyclic nucleotides in biological materials.

Hybridomas will be prepared through fusion of mouse myeloma cells with spleens of mice immunized with succinyl-cAMP (or cGMP) conjugated to bovine serum albumin. Resultant monoclonal antibodies will be attached to β-galactosidase and used in a rapid solid-phase enzyme immunoassay using fluorogenic substrates. These expected results will serve as the basis of Phase II, where the final assay format will offer valuable and novel tools for basic research. Additionally, such products will have significant commercial markets in research and clinical medicine, and may offer new diagnostic aids for the early detection of several disease and neoplastic conditions.

Title of Project: Monoclonal Antibodies and Immunoassay for E. Coli Toxin

Principal Investigator: Harvey J. Brandwein

Awardee Organization: Genetic Diagnostics Corporation
160 Community Drive
Great Neck, New York 11021

Telephone Number: (516) 487-4711

Recent advances in biochemistry and immunology now make possible new approaches for detection and treatment of infectious diseases.

The objective of this project is to develop a monoclonal antibody-based immunoassay for the Escherichia coli (E. coli) heat-stable enterotoxin (ST), which causes "traveler's diarrhea" in humans, and widespread, often fatal, infectious diarrhea (scours) in newborn livestock. Phase I goals will be (1) to generate a panel of murine monoclonal antibodies to the toxin, and (2) to commence development of a sensitive and versatile ST fluorescence immunoassay. Purified monoclonal antibodies will be conjugated to β-galactosidase and tested in a heterogeneous competitive assay format. Investigators will pursue solid-phase methods for immobilization of ST-albumin conjugates, which will then compete with the test sample for binding to antibody-enzyme conjugates. Enzyme activity (and subsequently, ST concentrations) will be measured in a fluorescence assay, monitoring the formation of methyl-umbelliferone from the nonfluorescent substrate, methyl-umbelliferyl galactoside. The final (fluorescence) measurements can be made in any appropriately set fluorimeter, or in a low-cost, portable photon-counting fluorimeter that investigators have been developing for use with such immunoassays. Both the instrument and the assay format are geared toward rapid, technically facile performance in a laboratory or "field" setting.

Due to the health and economic impact of toxin-related diseases, the investigators believe there are significant human and veterinary commercial markets for such a toxin detection method, as well as the possible commercial utility of such antibodies as therapeutic agents. Genetics Diagnostics Corporation is also well positioned to attract follow-on funding for this project and to develop/market such commercial products. The technology developed should also be applicable to other infectious diseases.

Title of Project:	Detection of Antibiotic-Resistance in Bacteria
Principal Investigator:	Milton R. Tam
Awardee Organization:	Genetic Systems Corporation 3005 First Avenue Seattle, Washington 98121
Telephone Number:	(206) 624-4300 extension 217

Isolation of penicillin-resistant strains of Neisseria gonorrhoeae and Haemophilus influenzae has increased substantially in the United States over the last few years. In some regions this rapid increase in the number of resistant strains has heightened the concern of public health agencies and has resulted in revised methods of control. If the spread of resistant strains is not controlled, this failure will be reflected in a higher incidence of disease and increased costs of treatment with alternative antibiotics. One improvement in the methods for control would be to provide a means of more rapid bacterial detection and identification of resistance factors. This method must be faster than the 2-4 days necessary for culture-dependent techniques but possess a similar degree of accuracy and sensitivity.

The investigators are developing a direct, culture-independent assay using monoclonal antibodies. Since resistance is conferred by unique, plasmid-encoded proteins (that is, β-lactamase) target molecules can be identified by a sensitive immunofluorescence assay to stain individual bacteria in a direct patient smear. For this purpose, monoclonal antibodies directed against two "functional" targets will be used. The first will provide the phylogenetic identification of the bacteria (that is, antibodies to membrane proteins or lipopolysaccharides), and the second will identify the specific plasmid-encoded resistance factor (that is, antibody to β-lactamase). A patient specimen will be smeared onto microscope slides, fixed, and stained with the antibodies. The slides will then be scanned under a fluorescence microscope for the presence of stained organisms. Since β-lactamase accumulates in the periplasmic spaces between the cell wall and outer membrane, it may be possible to identify the bacteria possessing the resistance factor by a characteristic staining morphology. It should be possible to perform the test in less than an hour with a degree of sensitivity and accuracy comparable to culture.

Title of Project:	**Baculovirus Vector: Expression of Genes in Insect Cells**
Principal Investigator:	**Wayne E. Gleiber**
Awardee Organization:	**Great Lakes BioScience** **Post Office Box 364** **505 Pleasant Street, Suite 311** **St. Joseph, Michigan 49085**
Telephone Number:	**(616) 983-3015**

The objective of this project is to develop cloning and expression vectors from nuclear polyhedrosis viruses (NPV) with capabilities for efficiently and simultaneously producing one of several genes through the isolation and engineering of at least two new polyhedrin gene promoters in infected insect cell cultures. Alternative plasmid transfer vectors with increased expression capabilities will be constructed in Phase I. These transfer vectors will be used in the construction of viral expression vectors capable of producing more than one gene product at one time under the control of polyhedrin promoters.

Phase II will concentrate on the expression of specified genes in the vectors, optimization of large-scale cultures of vector-infected insect cells, and purification procedures for the gene products. Preliminary studies have demonstrated that this expression system allows posttranslational modification, glycosylation, and efficient secretion of gene products from infected cells. During the course of this study investigators will also complete a detailed cost analysis comparing this system with classical bacterial and yeast expression systems. The new vectors developed in this study will enhance the commercial feasibility of NPV-infected cell cultures as efficient expression systems for many gene products that could be marketed as research and clinically therapeutic reagents.

Title of Project:	**Protective Immunity Against Gonococcal Infection**
Principal Investigator:	**John C. McMichael**
Awardee Organization:	**ImmunoMed Corporation** **4904 West Cypress Street** **Tampa, Florida 33607**
Telephone Number:	**(813) 879-5620**

The goal of this project is to develop a safe and effective vaccine for gonorrhea. Investigators are attempting to develop an in vivo model system for gonorrhea. The eye of the rabbit, particularly after some form of traumatization, is susceptible to infection and is the proposed model system. The investigators will then characterize the immune response to the pilar common antigenic determinant. In this part of the study the production of the different class immunoglobins will be achieved, reasoning that the production of secretory immunoglobins should be the most protective mechanism. The next step will be to determine the protective effect of the pilar common antigen against virulent Neisseria gonorrhaeae with different serotypes of pili. This will be carried out after the development of the in vivo animal model.

Finally, the common antigenic structures of N. gonorrhaeae will be analyzed and in the case of the pilar common antigenic sites the particular amino acid sequence will be investigated for protective activity. This project would be a prelude to actual testing of a pili subunit vaccine in humans.

Title of Project:	A Novel Microbial Cell Immobilization Procedure
Principal Investigator:	Carl W. Lawton
Awardee Organization:	Lawton Scientific, Inc. 52 Chapman Road West Hartford, Connecticut 06107
Telephone Number:	(203) 521-3241

Investigations are being conducted on a new cell immobilization procedure to produce unique biocatalysts using latex coatings on activated carbon. In contrast to previously tried methods, this method gives a porous support allowing rapid substrate and gas transfer, has a hard surface to avoid compression in large beds, and is dense to allow use in fluidized beds. Phase I studies are concentrating on (1) demonstrating the broad spectrum capabilities of this method by immobilizing two organisms (Saccharomyces cerevisiae and Bacillus subtilis) that are useful for producing recombinant DNA proteins and a monoclonal antibody-producing hybridoma (CPG hybridoma), (2) optimizing the procedure for the first two organisms, and (3) making short-term measurements of biocatalyst life. Product formation (ethanol, L-tryptophan, antibody) will be assayed by suitable analytical technique to indicate the success of the immobilization.

The major anticipated result from Phase I will be a proven method for the immobilization of three medically important microorganisms. This research will test the feasibility of the proposed concept and will allow investigators to gather in Phase II additional research data that can be used to design a commercial catalyst in Phase III. This technology provides the potential for the large-scale production of rDNA proteins and monoclonal antibodies.

Title of Project:	**Synthetic Hybridization Probes for Herpes Simplex Type 2**
Principal Investigator:	**Jerry L. Ruth**
Awardee Organization:	**Molecular Biosystems, Inc.** **11180-A Roselle Street** **San Diego, California 92121**
Telephone Number:	**(619) 452-0681**

The long-term goal of this research is to develop synthetic DNA hybridization probes to detect viral infections. DNA hybridization has proven highly effective in detecting viruses, but current methods for making DNA hybridization probes are expensive to put into commercial use since they depend on enzymatically modified cloned DNA. Synthetic DNA probes, complementary to known sequences, are relatively inexpensive to produce. These probes hybridize rapidly to specific target sequences in DNA or RNA and are more sensitive to mutations and strain differences than cloned probes. The specific goal of this research project is to develop an oligonucleotide-based test to detect Herpes simplex virus type 2 (HSV-2).

Phase I involves the synthesis and testing of normal and chemically modified oligonucleotides complementary to the HSV thymidine kinase gene. Phase I will determine the sensitivity and specificity of oligomer probes for filter-bound HSV sequences compared to cloned probes and their ability to differentiate HSV type 1 and 2.

Phase II will refine the use of isotopic and nonisotopic probes to detect HSV in clinical samples. Once such probes are fully tested clinical diagnostic probes for other sequences can be developed (for example, hepatitis B virus, Epstein-Barr virus, and cytomegalovirus).

Title of Project:	**Possible AIDS Diagnostic Test**
Principal Investigator:	**Kenneth J. Widder**
Awardee Organization:	**Molecular Biosystems, Inc.** **11180-A Roselle Street** **San Diego, California 92121**
Telephone Number:	**(619) 452-0681**

Since June 1981, over 700 cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported to the Centers for Disease Control. Most cases have involved homosexual or bisexual men; the remainder involved heterosexual men and women, Haitians, and intravenous drug abusers. The etiology of the disease is probably a variously transmitted biological agent. Patients with AIDS have evidence of cellular immunodeficiency with cutaneous anergy, reduced numbers and altered proportions of T-lymphocytes, and impaired lymphocyte transformation. Opportunistic infections and Kaposi's sarcoma occurring in these patients are likely due to acquired immunodeficiency analogous to treatment with immunosuppressive drugs.

A genetic deficiency of adenosine deaminase (ADA) has been causally associated with severe combined immunodeficiency disease (SCID). Patients with ADA deficiency are subject to recurring, chronic, varied infections to which they often succumb. Many have no detectable lymphocytes in peripheral blood or bone marrow. Cell-mediated immunity is severely impaired. T-cells defined by E rosettes are often absent and lymphocyte proliferative responses are severely limited.

Given the close clinical resemblance between AIDS and SCID, the investigators propose to measure ADA levels in erythrocytes of 20 to 30 AIDS patients in order to determine whether a clinical manifestation of the disease process is associated with a deficiency of ADA. During Phase I, the investigators propose to determine whether there is an ADA deficiency in circulating erythrocytes of AIDS patients. If so, the study will be expanded in Phase II and a convenient assay for adenosine deaminase will be developed as part of a rapid screening test for AIDS.

Title of Project:	DNA Hybridization in the Diagnosis of Infectious Disease
Principal Investigator:	David R. Scholl
Awardee Organization:	Molecular Diagnostics, Inc. 1 President Street Athens, Ohio 45701
Telephone Number:	(614) 592-5782

DNA hybridization probes specific for common pathogenic bacteria have been developed. The long-term objective of this research is the perfection of simple protocols and a kit using DNA hybridization probes for the detection and identification of pathogens in clinical specimens. The specific aim of this project is to assess the feasibility of this approach to pathogen identification in clinical specimens by: (1) determining numbers and methods of recovery of pathogens in clinical specimens; (2) assessing the facility with which they may be lysed and their DNA prepared for hybridization; (3) determining the utility of procedures developed for rapid hybridization; and (4) assessing probe modifications to enhance detectability. The methods employed include cloning and identifying bacterial DNA fragments with unique base sequences, developing procedures for lysing bacteria and recovering DNA, developing protocols for rapid DNA-DNA hybridization, and detecting hybrid complexes. Successful completion of Phase I will demonstrate that DNA hybridization procedures can accurately and quickly detect and identify pathogens in clinical material. With feasibility demonstrated, Phase II development will require the cloning and testing of additional probes specific for pathogens encountered in infectious disease, modifying and adapting procedures for different types of clinical specimens, and developing alternative methods for detection of hybrid complexes. The application of recombinant DNA technology to diagnosis of infectious disease represents a fundamental departure from current microbiological identification procedures and should provide unsurpassed accuracy in organism identification. Development of this procedure into a simple, reliable kit has major commercial potential.

Title of Project:	**Clinical Diagnostic Bioprobes for Antibiotic Resistance**
Principal Investigator:	**Bruce J. Bradley**
Awardee Organization:	**North West Labs, Inc.** **901 North Lincoln** **Jerome, Idaho 93338**
Telephone Number:	**(208) 324-7511**

A microcosm of pathogenic bacteria resistant to antibiotics has recently developed in a particular geographical area resulting from close confinement of pathogen-carrying animals from around the Nation. The investigators' laboratory routinely screens hundreds of clinical samples monthly for bacterial identification and antibiotic sensitivity.

In Phase I research, recent recombinant DNA technology will be applied to "salted" nonpathogenic or clinical specimens to demonstrate feasibility of rapid, accurate, and clinically rational drug susceptibility tests.

DNA probes for antibiotic resistant genes, labeled with biotin (Bioprobes) will be hybridized with microbial plasmid DNA using direct slide techniques or cellulose nitrate strips or dots to detect DNA sequences encoding resistance to ampicillin or tetracycline. Current preparatory procedures used in the laboratory will be refined to develop methods for rapid clinical specimen preparation, bacterial concentration, and Bioprobe application.

Hybridized Bioprobes will be detected with rabbit antibiotin and fluorescein labeled goat antirabbit antibody or with colorimetric procedures. More rapid and clinically rational applications of visualization techniques will be investigated. This animal model may provide prototypical methodology for improved clinical diagnosis and treatment of human disease.

Phase II research will expand Phase I technology toward commercial test "kits" for numerous resistant genes of various genera by rapid concurrent clinical procedures.

Title of Project: Rapid Single Virus Detection and Identification

Principal Investigator: Myron J. Block

Awardee Organization: ORD, Inc.
P.O. Box 50
Nahant, Massachusetts 01908

Telephone Number: (617) 592-3650

The objective of this project is to develop an optical instrument (using fluorescent antibodies) for viral diagnosis that is so sensitive, rapid, simple, and inexpensive that it will have wide research and diagnostic use.

The specific aim is to identify (within 10 minutes) a single virus in concentrations down to 10 viruses/milliliter in raw samples. This will be done in part by measuring the fluorescence from a single fluorescent antibody and simultaneously measuring the light scattering from a single virus to which it may be bound.

Title of Project: New Parenteral and Oral Antiparasitic Antimony Agents

Principal Investigator: Joseph A. Hoffman

Awardee Organization: Orphan Designed Drugs, Inc.
475 Rolling Hills Road
Bridgewater, New Jersey 08807

Telephone Number: (201) 722-6654

The specific aim of this project is to synthesize proprietary drugs to treat schistosomiasis, leishmaniasis, and trypanosomiasis parasitic diseases. The basis for this proposal is related to two technical assumptions that should greatly reduce the toxicity of antimony while enhancing the efficacy of the drugs. There are scattered references from the published literature suggesting these improvements.

Approximately 20 new trivalent antimony compounds will be prepared. Primarily they will be derivatives of carboxylic acids, hydroxy-carboxylic acids, and carbohydrates.

Besides reducing toxicity, another badly needed improvement in the therapeutic administration of antiparasitic drugs is to have the drugs taken orally rather than by inconvenient and painful subcutaneous or intramuscular injections. The structural modifications achieved by this project should result in more stable and bioavailable antimony compositions administered orally.

Title of Project:	**Synthesis of Lipophilic Penicillins**
Principal Investigator:	**Harold L. Sadoff**
Awardee Organization:	**Recomtex Corporation** **919 East Grand River Avenue** **East Lansing, Michigan 48823**
Telephone Number:	**(517) 332-1600**

The objective of this research project is to produce lipophilic penicillins or cephalosporins capable of crossing the blood-brain barrier. Such drugs will be valuable in the treatment of meningitis, particularly those caused by Hemophilus influenzae, Neisseria meningitidis, or certain groups of streptococci in neonates. They would constitute a new class of antibiotics and attract the immediate attention of several ethical pharmaceutical manufacturers. During Phase II the investigator would enter a development agreement with one such corporation.

The Phase I objectives are to prepare analogs of penicillin G in which its phenylacetate moiety is replaced by 5-methyl resorcinol, 5-pentadecylresorcinol, 5-heneicosyl-resorcinol, 6-n-heneicosyl-4-hydroxy-pyran-2-one, and 5-pentadecylphenol, compounds that render membranes permeable to certain ions and small molecules. In all cases, the phenoxyacetate of each of the above compounds will be synthesized and these compounds then will be coupled to 6-amino-penicillamic acid. The antibiotic potency of the penicillin analogs will be tested against both lacta mase-positive and negative strains of the agents causing meningitis. Preliminary toxicity studies will be conducted in mice injected with graded amounts of the lipophilic penicillins. The mouse brains will be extracted to determine the levels of "resorcinolic" antibiotics present relative to control penicillins or cephalosporins.

Title of Project:	**Automated Dose-Response Analysis**
Principal Investigator:	**Samuel Schalkowsky**
Awardee Organization:	**Spiral System Instruments, Inc. 4853 Cordell Avenue, Suite A10 Bethesda, Maryland 20814**
Telephone Number:	**(301) 657-1620**

This Phase I project is extending existing computer software and using it to analyze dose-response data obtained from bacterial interactions with selected antimicrobial agents. A proprietary method will be used to provide, from a single petri dish, data on bacterial population changes and colony size variation over a range of up to 600:1 in antimicrobial agent potency. Existing laser-scanning instrumentation will transfer plate measurements into the memory of developmental computer hardware for automated analysis of the dose-response data. Applicability of automated dose-response analysis derived from a single petri dish will be evaluated for antimicrobial and genetic damage assays. Significantly more and better information is anticipated for these and similar bacterial interaction processes, with substantial reduction in the cost--in time and materials--of these assays. Antimicrobial applications include validation of drug potency, of antibiotic levels in body fluids, and of susceptibility, particularly for drug combinations. Genetic damage applications are exemplified by the automated analysis of dose-response data containing both mutagenic (revertant) and toxic regions.

The Phase II program will develop detailed test methodologies and validate them in collaborative studies. Automated dose-response analysis will have broad marketability in microbiological testing.

Phase II Projects

Title of Project: Diagnostics Specific for Chagas' Disease

Principal Investigator: Elizabeth A. Dragon

Awardee Organization: Codon
430 Valley Drive
Brisbane, California 94005

Telephone Number: (415) 467-0740

Trypanosoma cruzi, a hemoflagellete, is the causative agent of Chagas' disease, a major health problem in Central and South America. It is estimated that at least 12 million individuals are infected with the protozoan parasite; 200 million people are exposed to the vector, a reduviid bug. The focus of this research is the application of recombinant DNA technology to the development of a more specific diagnostic test for Chagas' disease. Current serological diagnostics are insensitive and can cross-react with serum antibodies from individuals infected with other protozoan parasites, such as Leishmania.

During the Phase I stage of this project investigators identified a molecular weight 90,000 dalton surface protein from T. cruzi trypomastigotes and demonstrated that it could be used as a diagnostic antigen. cDNA libraries of T. cruzi trypomastigote poly (A+) mRNA were constructed. During the Phase II stage of this research, the investigators plan to identify the appropriate cDNA clones containing the gene for the 90,000 dalton antigen using immunological and/or oligonucleotide hybridization techniques. An expression vector containing the gene for the 90,000 dalton antigen will be constructed; the bioengineered diagnostic antigen will be used in the development of two types of diagnostic kits, an enzyme-linked immunosorbent assay (ELISA) and a latex agglutination.

Title of Project: Development of Palytoxin Immunotoxins

Principal Investigator: Douglas C. Vann

Awardee Organization: Hawaii Biotechnology Group, Inc.
c/o Hawaiian Sugar Planters' Association Lab
99-193 Aiea Heights Drive
Aiea, Hawaii 96701

Telephone Number: (808) 487-5561 extension 281

The objective of this project is to establish methods for conjugating the potent marine toxin, palytoxin, to antibodies in such a way that specific cytotoxicity of target cells is possible. The project, immunopalytoxin (IPT), will be tested in a variety of cultured cell and transplantable animal tumor models. It is expected that IPT will have unique properties that offer superiority to conventional immunotoxins. Cancer therapy, immune responses modulation, and specific cell ablation are important examples of medical applications of IPT.

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES

Phase I Projects

Title of Project: Miniaturized Hemodialysis and Peritoneal Dialysis Machine

Principal Investigator: Stephen R. Ash

Awardee Organization: Ash Medical Systems, Inc.
613 Ridgewood Drive
West Lafayette, Indiana 47906

Telephone Number: (317) 463-9540

The objective of this research project is to produce a portable, miniaturized dialysis machine that is simple, safe, and symptom-free in operation. This dialysis machine should allow the average hemodialysis or peritoneal dialysis patient to perform dialysis at home, unassisted. The machine will be small (12 pounds), portable, and totally self-contained (without need for connection to a water or electric current supply). To achieve this goal, Ash Medical Systems, Inc., will combine five technologies that have been developed at Purdue University in the last 8 years:

1. A zeolite-based sorbent suspension.
2. A novel method of operation of plate dialyzers using a sorbent suspension in dialysate.
3. A computer control system optimizing blood flow.
4. A highly sensitive Doppler ultrasound particle monitor.
5. Continuously operating chemical sensors.

The first phase of this project is to combine these individually proven technologies into a single, low-cost, simple dialysis machine. This dialyzer will allow single-button initiation of priming, dialysis, and rinsing (to a preset hematocrit level in the effluent). At the end of Phase I, a clinical prototype will be completed, and data on its efficacy and safety will be available to pursue FDA approval under Phase II.

Title of Project:	A Robotic Controlled Strength Training/Limb Mimic Device
Principal Investigator:	Keith R. Williams
Awardee Organization:	Athtec Systems 2221 Meadowbrook Drive Sacramento, California 95825
Telephone Number:	(916) 972-8977

This project is designing, developing, testing, and evaluating an innovative strength training system that incorporates both computer and robotic technology, to provide improved muscle rehabilitation therapy capabilities that are not currently available in the marketplace.

The initial design of the system will be a two-jointed robotic arm mounted on a floor-fixed base. The robotic arm will be attached to a patient's extremity, allowing the patient to make both active and passive movements applicable to a variety of planned rehabilitative, therapeutic, and/or strength training modes. The robot will be under the servo-control of a robotic computer capable of allowing specific patterns of movement and resistance.

These specific movement and resistance patterns will allow various strength training procedures to be adapted for each patient's therapeutic need. Therefore, the robot can be programmed to provide passive movement for a patient attempting to regain range of motion in a limb. Both the passive and active resistance movements will be safe for the patient, thus relieving the physical therapist from the therapeutic/rehabilitative exercise.

The potential for such a device in the physical therapy and rehabilitation market is tremendous. The system would be a major advance in the physical therapeutic and other rehabilitative settings. It would be an evaluation instrument as well as a systematic strength training system with more versatility and patient safety than currently available. The robotic components of the system would allow a therapist to set a basic exercise protocol for a patient, then be free to work with other patients, as the device would take over much of the therapist's time-consuming activity of manipulation and monitoring.

Title of Project:	**Colorimetric Urine or Sweat Osmolarity Test**
Principal Investigator:	Daniel A. Kerschensteiner
Awardee Organization:	Daniel Kerschensteiner and Associates 76-Q Farm Road Hillsborough, New Jersey 08876
Telephone Number:	(201) 874-5846

The purpose of this project is to establish the feasibility for a new concept of measuring sweat and urine osmolarity. This measurement is valuable as an aid in identifying cystic fibrosis in infants and also for monitoring salt intake in hypertensive individuals. Both of these tests are commercially desirable.

This test is based on a proven but proprietary method that employs an osmolarity-sensitive reactant and a special dye that changes color in response to small changes in ionic strength. A qualitative test and a semiquantitative test, as simple and as easily read as currently available pH dip stick tests, are envisioned for Phase II.

Phase I of the project is a survey and an identification of the best combination of reactant and dye; then, their performance will be tested under controlled conditions using the normal levels of the electrolytes found in sweat and urine. Once a working liquid formulation is discovered, the reagents will be dried in a film or on paper for potential use in a dip stick or slide-type arrangement.

Title of Project: Binding of Invertase to Macrophage Receptors

Principal Investigator: Henry E. Blair

Awardee Organization: Genzyme Corporation
75 Kneeland Street
Boston, Massachusetts 02111

Telephone Number: (800) 332-1042

The goal of this project is to use the yeast S. cerevisiae as a vector to synthesize cloned human lysosomal enzymes with a specific oligosaccharide that will target the enzymes to tissue macrophages. This may form the basis of a novel enzyme-replacement therapy for several inherited lysosomal storage diseases, as the dual problems of effective targeting and large-scale, low-cost production of replacement enzymes would be solved.

The yeast enzyme invertase will be used as a model for such studies. Certain yeast mutants with temperature-sensitive blocks in the secretion pathway should accumulate invertase intracellularly with defined asparagine-linked oligosaccharides with eight or nine mannose residues per chain. Both wild-type and modified invertases will be purified and characterized, and their ability to bind to rat alveolar macrophage mannose receptors will be tested. If time permits, tests on whether they are targeted to hepatic macrophophages after injection into rats will also be made.

Title of Project: Quantitation of Glycosylated Hemoglobin by Immunoassay

Principal Investigator: Daniel B. Cawley

Awardee Organization: Hybridoma Sciences, Inc.
4690 Hammermill Road
Atlanta, Georgia 30084

Telephone Number: (404) 493-1902

The measurement of glycosylated hemoglobin is probably the best means of assessing glucose control over time in diabetics. It now appears there is an inverse correlation between the control of glucose metabolism and complications of the disease in that well-controlled diabetics do much better. The current assay systems for quantitating glycosylated hemoglobin are bulky, time consuming, and expensive, and therefore are ideal candidates for replacement with a monoclonal antibody-based immunoassay.

To that end, antibodies from hybridoma clones derived from fusions of spleen cells from mice immunized with the glycosylated hemoglobin are being evaluated. The development of additional hybridomas is planned as part of Phase I. During Phase II, a two-site immunometric assay will be developed for quantitation of glycosylated hemoglobin for use in the clinical laboratory.

Title of Project:	Portable Orthopedic ElectroMagnetic (POEM) System
Principal Investigator:	Sheldon S. Thaler
Awardee Organization:	Geomed, Inc. 141 Union Avenue Middlesex, New Jersey 08846
Telephone Number:	(201) 560-3438

The POEM program is developing a patient-oriented/lightweight portable stimulator for treatment of hip disorders. The program is a derivative of basic research in this area by Drs. Lechner, Bassett, and others. The thrust is to produce a simplified battery-operated, easy-to-use device suitable for clinical applications. Present devices are line-operated and inconvenient to use over the long duration of the recommended therapy.

The basic design encompasses the two proven modalities of electromagnetic stimulation, that is, the pulsed stimulator of low duty cycle, and the low frequency continuous system. Portability will result from proprietary energy recovery circuitry. The program will also evaluate a clinically equivalent alternative waveshape with lower power requirements. The accomplishments of this program will also be relevant to existing electromagnetic stimulator therapy, which heretofore was concerned primarily with fracture healing.

Phase I will be concerned with evaluation and design of prototype units. Clinical progress in the area of electromagnetic hip therapy has been held back by the absence of a convenient, simple, patient-oriented device, and the proposed POEM system will satisfy the needs of the clinician. The success of electromagnetic therapy in treating femoral head and artificial joint disorders will be a major medical accomplishment.

Title of Project:	Implantable Glucose Sensor
Principal Investigator:	Jose D. Giner
Awardee Organization:	Giner, Inc. 14 Spring Street Waltham, Massachusetts 02154
Telephone Number:	(617) 899-7270

The objective of the research is to improve the sensitivity and selectivity of a catalytic metal electrode for determining glucose in biological fluids. Such improvement could lead to the development of an implantable glucose sensor that could provide a much greater degree of control of glucose levels in diabetics than is now possible. Such control would improve therapy for one of the world's major health problems.

Glucose sensor work using a catalytic metal sensor based on platinum is currently being performed. Using a newly discovered measurement technique, a sensor with sufficient accuracy and response time to function as an implantable alarm monitor has been developed. For more demanding applications (for example, to control the infusion of insulin by a pump), however, improvements in the accuracy of the sensor will be required. One approach involves the use of an electrode material with greater catalytic activity for the electrochemical oxidation of glucose, and/or lesser activity for the oxidation of any endogenous coreactants. Another involves the use of an electrode material that responds only to endogenous coreactants so that a correction for these coreactants can be made.

Title of Project:	Infrared Fiberoptics for CO_2 Laser Endoscopy
Principal Investigator:	Mir A. Ali
Awardee Organization:	Glass and Ceramics International, Inc. 2017-2019 Lomita Boulevard Lomita, California 90717
Telephone Number:	(213) 530-3279

Currently, commercial endoscopes use visible glass fiberoptics and operate in the visible region of the spectrum. High-energy lasers have shown promise as a means for developing localized blood coagulation with close control over the penetration of tissue necrosis. CO_2 laser transmitting at 10.6 microns has the potential for cautery in the gastrointestinal tract and thus can reduce and possibly avoid the need for expensive coagulants and blood transfusion.

Currently, infrared transmitting glasses (2-14 microns region) are commercially available. They must be fiberized to diameters such that they can be coupled with commercial (visible) endoscopes.

Phase I is a feasibility study in which commercial infrared transmitting glasses and polymers are screened and evaluated for possible impurities and toxic constituents, and their fiberizing characteristics are established. Suitable materials will be made into fiberoptics, and their potential as infrared fiberoptics for CO_2 laser endoscopy will be evaluated. Problems associated with coupling the infrared fiberoptics with commercial (visible) endoscopes will be established.

Phase II will be the development, test, and evaluation effort for an infrared fiberoptic CO_2 laser endoscopy system. Its potential for commercialization will be explored in Phase III.

Title of Project:	Development of Wearable Artificial Kidney
Principal Investigator:	S.T. DiNovo
Awardee Organization:	Guild Associates, Inc. 5625 North High Street Worthington, Ohio 43085
Telephone Number:	(614) 885-2962

This project is intended to demonstrate the technical feasibility of developing a truly wearable, continuously functioning artificial kidney by means of advanced adsorption technology.

The technical objectives for Phase I are to: (1) demonstrate experimentally the feasibility of separating urea into two simple aqueous models of dialysate or filtrate; (2) formulate a mathematical model of the system to provide predictions of performance; and (3) establish an equipment-based rationale for the ultimate size achievable with this technology.

These objectives, when achieved, will provide a solid basis for more extensive research and development in Phase II and eventual entry into commercial markets.

Preliminary calculations using urea as the key solute indicate sorbent requirements of fewer than 100 grams and reservoirs totaling slightly more than 1 liter. Given these parameters, the assembly should weigh under 10 pounds. By developing a means by which the adsorbent as well as the dialysate is continuously regenerated, waste products can be removed more effectively. Like the natural kidney, the proposed system is relatively nonspecific and inefficient, but simple, compact, and effective.

Title of Project:	**Vitamin Mineral Data Bank**
Principal Investigator:	Avalon Dungan
Awardee Organization:	JWK International Corporation 7617 Little River Turnpike Annandale, Virginia 22003
Telephone Number:	(703) 750-2500

The objective of this project is to establish an accurate vitamin and mineral data base that can be updated easily and can serve as the comprehensive reference for monitoring individuals' supplemental vitamin and/or mineral consumption. It addresses the need to improve methods for assessing nutrient intake. Earlier studies suggest that supplementation contributes significantly to the nutrient intake of about one-third of the population. The project capitalizes on the unique nature of the Universal Product Code marking, which appears on practically all common vitamin/mineral preparations as well as other more exotic dietary supplements such as bone meal and kelp.

Building on the data base developed earlier in a pilot study, the first step in this effort is to update and complete the identification of nutritional supplements with a Universal Product Code. Nutrient information for each item will also be converted through the computer so that dietary intake information will be expressed on the same basis regardless of the manufacturer's labeling information.

The Phase II follow-on will test the utility of the data bank through a survey of the use of nutritional supplements using a national probability sample and/or a targeted respondent sample such as participants in chemoprevention trials. Phase III will involve marketing the data base.

Title of Project:	Automated Instrument for Percutaneous Discectomy
Principal Investigator:	Carl C.T. Wang
Awardee Organization:	Medical Instrument Development Laboratories, Inc. 2999 Teagarden Street San Leandro, California 94577
Telephone Number:	(415) 352-9040

Back pain ranks second only to the common cold as a cause of time lost from work. Some back pain may be diagnosed as lumbar disc disease and may require medical treatment, which can include total disc removal by partial hemilaminectomy or chemonucleolysis.

To reduce the morbidity and expense of disc surgery and the dangers inherent in chemonucleolysis, an automated percutaneous discectomy instrument is greatly needed. The Phase I objective of this research project is to investigate the technical feasibility of developing an automated suction and cutting instrument for percutaneous removal of herniated disc material.

Title of Project:	Human Gallstone Dissolution with Silicones
Principal Investigator:	Robert R. LeVier
Awardee Organization:	Ventec Laboratories, Inc. 2284 Enterprise Drive Mt. Pleasant, Michigan 48858
Telephone Number:	(517) 773-2334

The ability of selected silicone-based polymers to dissolve human cholesterol and bilirubinate gallstones in vivo is being assessed. Gallstones are categorized as predominately cholesterol type or bilirubin type based on color. Weight-matched sets of four stones will be incubated in buffer, sodium cholate, mono-octanoin, and a series of silicone-based polymers. Weight loss will be followed by up to 3 weeks. Any polymer that compares favorably to mono-octanoin with regard to the dissolution rate for cholesterol stones will be suggested as a candidate for Phase II study. Polymers that dissolve bilirubinate stones at any rate will be considered candidates for Phase II study.

One polymer has been shown to promote the dissolution of bovine bilirubinate stones in a brief in vitro experiment. Phase II research will be directed toward preclinical qualification sufficient to warrant investigational new drug investigation of a safe polymeric solvent for bilirubinate stones that is compatible with mono-octanoin. Such a mixed solvent has potential to dissolve all retained gallstones.

Title of Project:	**Assay, Production, and Purification of Erythropoietin**
Principal Investigator:	**Peter P. Faletra**
Awardee Organization:	**North Valley Farms, Inc.** **3 Bancroft Park** **Hopedale, Massachusetts 01747**
Telephone Number:	**(617) 478-0948**

Erythropoietin (EP) is a primary regulator of erythropoiesis. Accordingly, its possible diagnostic and treatment applications in certain refractory anemias has been postulated. The lack of both raw material for erythropoietin purification and relatively pure EP (150 units per milligram of protein) has severely compromised its use in research, diagnosis, and treatment. This situation has been complicated by the lack of an accurate, simple assay for biologically active EP. The long-term objectives of this investigation are the development of economical procedures for the generation, assay, and purification of erythropoietin.

Using sheep and a novel blood plasmapheresis procedure, it is believed that large volumes of EP-rich plasma (2-10 units per milliliter) can be economically produced. This approach will allow for a low-cost supply of plasma for EP assay and purification. The in vitro plasma clot technique for culturing erythroid progenitors will be refined and developed as an erythropoietin bioassay. Purification will initially rely on a simplified partial purification procedure based on nitrocellulose-EP binding affinity and standard purification procedures to yield a pure enough EP antigen to generate highly specific EP-antisera (polyclonal and/or monoclonal). This could in turn be used to efficiently purify erythropoietin.

Title of Project:	Improved Wear Resistance of Implant Titanium Alloy by Ion Implantation
Principal Investigator:	Piran Sioshansi
Awardee Organization:	Spire Corporation Patriots Park Bedford, Massachusetts 01730
Telephone Number:	(617) 275-6000

Titanium alloys offer superior corrosion resistance, mechanical strength, lower elastic modulus and specific weight, and biocompatibility. The lower wear/abrasion tolerance of titanium, however, has hampered its full-scale application in orthopedic surgery. For long-term reliability of the titanium implant, the wear characteristic of the alloy must be modified. Advances in the technology and metallurgy of ion implantation have potential applications in surface modification of materials. Current literature demonstrates that tribological behavior of materials can be improved, in certain cases dramatically, by using this ion implantation technique.

This project is applying the technique to the improvement of wear resistance of titanium alloy. A successful program will (1) allow the use of the alloy in higher wear joints like the knee, (2) provide a better prosthesis/bone interface, and (3) lead to lower corrosion rates and less metal ion dissolution than cobalt alloy. It can therefore be expected that improved wear resistance, coupled with the excellent material properties of titanium, will lengthen lifetimes, improve the reliability of the implant devices, and make the benefits of orthopedic surgery available to younger patients who suffer damaged or diseased joints.

In this feasibility study, experiments are designed and performed to establish the technical merits of the processing technology. Physical metallurgical principles and experiences with other alloy systems will guide this research.

Title of Project:	A Simple Device for Assessing Nutritional Status
Principal Investigator:	Fraser J. Walsh
Awardee Organization:	Tracer Technologies, Inc. 225 Needham Street Newton, Massachusetts 02164
Telephone Number:	(617) 964-4800

The use of ^{13}C-labeled tracers in nutritional status assessment has recently received increased attention. Breath tests using low-cost ^{13}C-labeled tracers are emerging, along with metabolic monitoring breath tests in general, as useful clinical tools in the study of nutritional disorders in an outpatient setting. In such tests, the $^{13}CO_2/\ ^{12}CO_2$ is measured in breath following ^{13}C-labeled tracer ingestion; the rate and amount of $^{13}CO_2$ release can be used as a quantitative measure to discriminate between normals and patients. A limiting factor to the routine use of such patient-easy tests is the absence of a convenient, low-cost analytical tool for measuring $^{13}CO_2/^{12}CO_2$ in breath.

The Phase I program will provide the data required to initially validate the use of a new IR-based instrument for direct measurement of $^{13}CO_2/^{12}CO_2$ in breath. This new ratio infrared spectrometer (RIS) uses a highly reflective light pipe as a low- volume (5 cubic centimeter) sample cell. The infrared source is directed at a slight angle to the axis of this light pipe; the light pipe thus also serves as a long-pass White cell without the bulk and cost normally associated with such a cell. A beam splitter and three pyroelectric detectors are used in the RIS to give simultaneous measurement at $^{13}CO_2$, $^{12}CO_2$, and reference wavelengths. Initial work done by TRACER with the RIS has shown its repeatability in sample measurement to be 1.3 APE for ^{13}C over the CO_2 range of 2 to 6 volume percent.

In Phase I, the RIS will be modified to permit use of a low-volume (25 cubic centimeter) gas syringe as a sampling device. Using this modified device, correction algorithms will be developed to account for the observed nonlinearity in CO_2 response; these algorithms will be verified using reference samples analyzed by a ratio mass spectrometer (RMS). Initial validation of the RIS as the instrument of choice in breath tests for screening in nutritional status assessment will be undertaken using breath samples from normals and patients. In Phase II, in-field RIS validation will be carried out in collaboration with clinicians presently evaluating breath tests in nutritional status assessment.

Title of Project:	Multisensor Esophageal Probe and Portable Monitor
Principal Investigator:	Laughton E. Miles
Awardee Organization:	Vitalog Corporation 2484 Old Middlefield Way Mountain View, California 94043
Telephone Number:	(415) 968-6900

The goal of this project is to develop a small, easily inserted intraesophageal probe containing three pH sensors, two pressure transducers, and a single liquid infusion channel. This probe will be low cost and durable, and safely and easily tolerated by most patients for up to 48 hours at home and at work. It will interface with a small, portable autoinfusion device and a portable, programmable microcomputer with multiple sensor inputs (including a patient event marker), capable of recording continuously for more than 1 week on a single battery charge.

The proposed system will be useful for the evolution and management of gastro-esophageal reflux and esophagitis, abnormal esophageal motility, obscure chest pain, pulmonary disease caused by silent esophageal reflux, sudden death syndrome, and obscure nocturnal attacks.

Phase II will be directed toward clinical testing, validation, and design iterations.

Phase II Projects

Title of Project:	Magnetometer for Human Iron Stores Assessment
Principal Investigator:	Duane B. Crum
Awardee Organization:	Biomagnetic Technologies, Inc. 4174 Sorrento Valley Boulevard San Diego, California 92121
Telephone Number:	(619) 453-6300

Measurement of iron stores can act as an indicator of various serious disorders. Stored iron overload or deficiency suggests further examination and possible therapy. Indirect means of measuring iron stores lack sensitivity or specificity, while available direct measures are invasive, discomforting, and in the case of liver biopsy, risky. Pioneering work using magnetometers demonstrated the technical merit of a new noninvasive technique known as biomagnetic susceptometry. Clinical studies, however, have been limited to iron overload because of inadequate resolution in existing instrumentation.

In Phase I of this program, factors limiting instrument resolution were identified and techniques were developed to provide the improved performance required to measure iron deficiency and monitor small changes in iron overload that occur during therapy. Phase II will design, fabricate, and clinically validate a complete prototype system for a commercially marketable instrument capable of safe, accurate, noninvasive measurement of hepatic iron stores over the entire range of physiological significance. This effort involves extensive preliminary research and development aimed at improved pickup coils, more accurate methods of data analysis, new measurement procedures, modifications to the magnetometer support and water-filled coupling membrane, and other important refinements.

Title of Project:	Cost Effective, Non-Invasive Bladder Volume Instrument
Principal Investigator:	David Giuliani
Awardee Organization:	Biomedics, Inc. Post Office Box 971 Mercer Island, Washington 98040
Telephone Number:	(206) 392-8391

The aim of this project is to develop a noninvasive, easy-to-use, low-cost, portable instrument for measuring the volume of urine in the bladder using nonionizing ultrasonic energy. The device will display the computed volume directly on a digital display, thus eliminating the need for image interpretation by specialists.

Currently, catheterization is the only technique for measuring the volume of retained urine. However, this is an invasive procedure associated with significant trauma and risk of infection to the patient. This new instrument will obviate the need for such a procedure. Moreover, because it is portable, it will be readily available for monitoring critically ill, nonambulatory patients.

This device has the potential for extensive use by urologists, spinal cord injury centers, hospital recovery rooms, and postoperative nursing floors.

Phase I has proved the feasibility of an experimental version by testing it against catheterization-derived measurements. Phase II will consist of refining and testing the instrument over a wider spectrum of clinical settings so that it can evolve into the product prototype.

Title of Project:	Laser for Photomedical Selective Photothermolysis
Principal Investigator:	Horace W. Furumoto
Awardee Organization:	Candela Corporation 96 South Avenue Natick, Massachusetts 01760
Telephone Number:	(617) 653-7373

This project is developing a medical laser device to meet the requirements of selective photothermolysis (SPT). SPT is a target-specific laser radiation treatment that leaves tissue surrounding the target unaffected. Selectivity is achieved by using laser radiation of appropriate wavelength, pulse duration, and energy density.

The Phase II program will develop a medical laser device for treatment of port wine stain (PWS) birthmarks. Phase I studies showed that dermal blood vessels can be severely damaged without altering the epidermis, appendages, fibroblasts, or other cells. SPT treatment of PWS using lasers developed under Phase I may displace existing argon laser techniques. Current findings suggest that SPT is PWS lesion-specific; therefore, SPT therapy will reduce the chance for negative side effects. It will also provide treatment to patients now considered unsuitable for argon laser treatment. Pilot clinical studies, although very preliminary, corroborate these conjectures.

The Phase II program will cover continuing laser research and development, assembly of two new investigational laser devices, and a fully engineered medical laser device. It will also support research at the Massachusetts General Hospital in Boston, Massachusetts, to apply SPT to clinically useful purposes.

Title of Project:	Computerized Bio-Chrono-Monitor and Decision Helper
Principal Investigator:	Brian P. Brockway
Awardee Organization:	Data Sciences 6009 Wayzata Boulevard Suite 110 St. Louis Park, Minnesota 55426
Telephone Number:	(612) 546-8756

This project is enhancing the data acquisition system developed in Phase I by adding new software and hardware features and by developing an implantable device for telemetric monitoring of blood pressure in rats. Communications capability will be added for transmitting acquired data to a computer using a standard communications protocol. In addition, the data base generated by the IBM personal computer will be linked with a standard spreadsheet and data base manager so that spreadsheet operations may be performed on the computer concomitant with data acquisition. These two enhancements will provide a great deal of versatility in handling acquired data. Online spreadsheet capability will allow someone with a very limited knowledge of computer programming to write customized applications programs to process data.

In addition to these enhancements of existing hardware and software, an intelligent implantable data acquisition and telemetry system for long-term monitoring of small animals will be developed. The electronics will be designed to accommodate simultaneous collection of data from three variables; however, since the device is targeted for use in rats, the packaging will accommodate only blood pressure measurements. Blood pressure was chosen because of the wide-ranging utility such data offer to a number of areas of investigation, the potential market size of the product, and the lack of commercially available devices for telemetric monitoring of blood pressure in animals this small.

Title of Project:	Computer Enhancement of Diabetes Self Care (DIACARE)
Principal Investigator:	Alan K. Kronhaus
Awardee Organization:	Kron Research and Consulting Corporation c/o KRON Medical Corporation 1829 East Franklin Street Chapel Hill, North Carolina 27514
Telephone Number:	(919) 968-4881

Phase I of this project developed hardware (DIACARE Monitor) and software (DIACARE Patient Program and Host Computer Program), which collects blood glucose and other relevant data from patients at home. The system allows for periodic transfer of stored information to a central computer over the phone using a modem. Phase II will field test the DIACARE Home Glucose Monitoring System. Eighty patients with insulin-dependent diabetes mellitus will be recruited from two large diabetology practices and four general internal medicine practices. Patients will record blood glucose and other data using the DIACARE Monitor, and transmit these data once a week by phone using a modem to the DIACARE Central office. A host computer in the DIACARE Central office will in turn issue a monthly report summarizing the data collected to both the patient and the physician. An automated insulin adjustment program will be tested to determine if it adds incrementally to diabetes control in patients using the DIACARE system.

Title of Project:	Evaluation of an Artificial Colon Sphincter
Principal Investigator:	Charles D. Baker
Awardee Organization:	Technical Research Associates, Inc. 410 Chipeta Way Salt Lake City, Utah 84108
Telephone Number:	(801) 582-8080

The Phase II evaluation is observing the results of applying a constriction device of novel design on the colon of test animals. The device will provide an alternative to the Erlangen plug and the standard stoma surgery, which requires a bag set adhesively to the skin. With the device, the patient will be able to open or close the colon on demand, alleviating many existing physical and psychological problems. Phase I showed the basic feasibility of applying constricting cycles in the colon and provided design data needed to fabricate candidate devices. Phase II involves detailed animal experiments to establish the safety and efficacy of the device for colon cancer stoma patients.

NATIONAL CANCER INSTITUTE

Phase I Projects

Title of Project:	A Low-Cost Morphometry-Stereology System
Principal Investigator:	Jose R. Torre-Bueno
Awardee Organization:	American Innovation, Inc. 1009 Urban Avenue Durham, North Carolina 27701
Telephone Number:	(919) 688-8466

Morphometric techniques are becoming increasingly indispensable in many fields, including microanatomy, pathology, and physiology. Computer-based morphometry systems greatly facilitate the collection and analysis of the large volumes of data required for a meaningful statistical analysis. Systems of this type currently cost $12,000-$20,000, largely because they may require semicustom hardware and because the cost of software development is spread over a small customer base. However, the appearance of inexpensive and capable microcomputers such as the Commodore 64 in the mass market, makes it possible to design a morphometry system in which the parts cost could be as low as $900. If the software development costs were spread over a large number of customers, a powerful morphometry system could be sold for as little as $2,500.

This project envisions a system based on the Commodore 64, which would work with either video images or photographs and allow the user to indicate points or lines with a light pen or a digitizing pad. The system would then store these data to a floppy disk for later processing by a library of morphometric and stereologic programs.

Title of Project:	Developing a Health Information and Promotion Service
Principal Investigator:	Norma J. Goodwin
Awardee Organization:	AMRON Management Consultants, Inc. 3020 Glenwood Road Brooklyn, New York 11210
Telephone Number:	(212) 434-0986

The objective of this research project is to develop a Health Information and Promotion Service focusing on increasing the knowledge and understanding of the black population about cancer, and modifying behavior to decrease its disproportionately high incidence. Specific aims are:

1. determining the feasibility of black organizations serving as vehicles for implementing this initiative;

2. ascertaining corporate, foundation, and labor union interest in purchasing products and services for the target population, especially the economically disadvantaged;

3. delineating promotional and marketing materials and approaches likely to be effective, especially for those at highest risk; and

4. determining the feasibility of the service becoming a commercially viable business.

Existing information concerning black perceptions, attitudes, and knowledge about cancer will be analyzed, and structured telephone interviews will be conducted with 100 organizational leaders.

Phase I findings will provide insight into: (1) the requirements for materials development; (2) the potential utility of state-of-the-art marketing approaches; and (3) the feasibility of the organizational roles projected. These findings will set the framework for Phase II, which entails expanded market research, financial feasibility study, and product and service development.

Title of Project:	Wearable Non-Gravity-Dependent Infusion Device
Principal Investigator:	Anatole J. Sipin
Awardee Organization:	Anatole J. Sipin Company, Inc. 505 Eighth Avenue New York, New York 10018
Telephone Number:	(212) 695-5706

The objective of this project is to develop a miniature, nongravity-dependent infusion device that is small and light enough to be worn.

One important application for a wearable infusion device is for total parenteral nutrition. A reliable, wearable infusion device could free patients for varying periods of time from attachment to existing, bulky infusion pumps and thus improve their quality of life.

Other applications could be for enteral feeding, continuous drug infusion, chemotherapy for cancer patients, and continuous delivery of insulin to diabetics. The device could also be valuable for patient transport and for ordinary intravenous infusion procedures.

The approach is twofold, providing a container for the intravenous (IV) fluid in which the fluid can be pressurized through a flexible barrier and that can be oriented in any position; and a means to pressurize the IV fluid within the container with air to maintain a constant flow of fluid. Advantages are that a standard IV infusion set is used; the flow rate is independent of the container position; and the pumping device is small and light enough to be wearable.

Title of Project:	A Human Liver Cancer Serum Marker
Principal Investigator:	James H. Hillman
Awardee Organization:	Antibodies Incorporated Post Office Box 1560 Davis, California 95617
Telephone Number:	(916) 758-4400

The development of a sensitive, rapid, and relatively inexpensive serum assay for specific forms of cancer would be invaluable for the early diagnosis of the cancer, its subsequent treatment, and studies on the etiology and epidemiology of the disease. While not a diagnostic panacea, the serum assay could quicken diagnosis and aid in followup on the progression or regression of the neoplasm.

In Phase I, this project is developing an immunochemical assay for human serum epoxide hydrolase-preneoplastic antigen in order to facilitate studies on this assay as a specific test for hepatocellular carcinoma in humans. The specific aims for Phase I are: (1) to isolate epoxide hydrolase-preneoplastic antigen (EH-PNA) from liver microzomes of a primate, (2) to use the isolated EH-PNA as an antigen to induce antisera in goats and rabbits, (3) to make the antisera (immunoglobulin G fraction) monospecific for EH-PNA, and (4) to develop an enzyme-linked-immunoabsorbent-assay (ELISA) for EH-PNA applicable to human sera.

The cancer with the highest mortality rate, liver cancer, has an etiologically predisposing population of millions who suffer from hepatitis B, cirrhosis, and other chronic liver diseases. Based on laboratory studies, a protein (EH-PNA) has been described that is released from its membranous environment, especially in preneoplastic and neoplastic liver cells of rodents. A sensitive radiochemical assay for EH-PNA developed at the University of California has now provided evidence that elevated EH-PNA appears in the serum of patients with hepatocellular carcinoma. Using antibodies against rat epoxide hydrolase, a rapid (ELISA) has been developed demonstrating the applicability of this technique for measuring EH-PNA.

The immunochemical assay for EH-PNA in human serum will involve work under a licensing agreement on an invention by the University of California (the measurement of serum EH-PNA) for which a patent application has been made. This will allow Antibodies, Inc. to pursue specific research that may lead eventually to the rights for production and marketing of the assay kit. The kit would then be distributed for use in studies on the efficiency of the assay, which will provide the basis for Phase II of this project. Collaboration with the University of California will occur on scientific aspects of the assay.

Title of Project:	Two-Wavelength Laser for Surgery
Principal Investigator:	Robert T. Kung
Awardee Organization:	Applied Biomedical Corporation 33 Cherry Hill Drive Danvers, Massachusetts 01923
Telephone Number:	(617) 777-5410

Lasers have been used as a surgical modality in recent years. Lasers of various wavelengths are suited for different specific surgical functions. CO_2 (10.6 micron) radiation has small penetration depths in tissues, leading to high surface temperatures that are desirable for tissue incision through evaporation. Nd:YAG lasers (1.06 micron) provide volumetric tissue heating, which is effective in vascular coagulation. In the treatment of tumors and cancerous tissues, concurrent hemostasis and incision are requirements for widespread clinical applications of lasers as surgical tools. The specific aim of this project is the development of a new surgical laser system capable of providing all these functions. The overall objectives of Phase I are twofold: (1) to design and analyze a laser system capable of delivering the necessary powers at 1.06 micron and 1.9 micron and (2) to conduct experiments to determine tissue absorption and interaction characteristics at 1.9 micron, thus verifying the power levels necessary for incision.

The system has the advantages of a single power supply and one laser head. It can also cut, which Nd:YAG alone cannot do. It should accomplish hemostasis of vascular regions where CO_2 is not adequate. In addition, an important feature is its compatibility with conventional quartz fiberoptics delivery system. Such a laser will have widespread clinical applications and commercial potential.

Results from Phase I will provide the basis for a Phase II program to fabricate this laser and conduct in vivo animal experiments.

Title of Project:	Feasibility Studies for Flying-Spot Infrared Scanning
Principal Investigator:	William L. Dunn
Awardee Organization:	Applied Research Associates, Inc. 2101 San Pedro Boulevard, Northeast Suite A Albuquerque, New Mexico 87110
Telephone Number:	(919) 876-0018

The objective of this study is to examine the feasibility of designing an infrared scanner by applying the well-known "flying-spot" principle, which rejects image-degrading scattered radiation, to transmitted infrared (IR) imaging of thin body parts such as the female breast. Such examinations now rely on wide (and thus scatter-rich) beams of visible light. The advantages of such a scanner, in spite of its poor spatial resolution, are expected to include (1) improved contrast because of scatter rejection, (2) sensitivity to certain chemical and physical properties of tissues, (3) effectively real-time output with no IR film processing, (4) availability of digital output, facilitating, for example, contrast enhancement and multiwavelength techniques, (5) daylight operation, (6) complete absence of risk, so far as is known, except for an easily-managed ophthalmological hazard, and (7) model cost, portability, and elimination of special examination rooms. Items 6 and 7 would facilitate use in mass screening.

Calculations will be carried out using both the facile method (lately extended to three-dimensional radiation transport and the Monte Carlo technique of nearinfrared transmission through plane-parallel slabs exposed to pencil beams (diameter 1 millimeter). The calculations are expected to give extensive information on penetration and scattering as a function of wavelength, including the radial and angular distributions of the emergent flux. A limited experimental program will check the calculations where input data are available and will seek to provide basic attenuation information where such data are lacking as a starting point for computation.

The project is likely to provide feasibility and design information on a device whose clinical and commercial possibilities are considerable, without the expense and risk of a full developmental study. Phase II and/or other funding will be sought if feasibility is established in Phase I.

Title of Project:	Bioerodible Polymers for Controlled Drug Delivery
Principal Investigator:	Kelly L. Smith
Awardee Organization:	Bend Research, Inc. 64550 Research Road Bend, Oregon 97701-8599
Telephone Number:	(503) 382-4100

The ultimate objective of this research project is to develop bioerodible polymer-drug implants that can be used for either long-term systemic or localized drug delivery. The specific aims of the Phase I program involve characterizing the drug loading and drug molecular weight range that can be used with a newly developed class of bioerodible hydrogels. The Phase I program includes synthesis of several types of these polymers containing drugs with a range of molecular weights, and subsequent determination of drug-release kinetics in vitro.

It is expected that the results of this work will define both the lowest molecular weight and highest loading of drugs that can be released by erosion of the polymer. This will enable the selection of specific drug/polymer products to be developed and tested both in vitro and in vivo in Phase II. These products could include such commercially important drugs as human growth hormone, luteinizing hormone releasing hormone, calcitonin, insulin, interferon, heparin, enzymes, antibiotics, antineoplastics, antigens, and narcotic antagonists. The development of bioerodible implants containing such drugs could result in dramatically improved drug efficacy while avoiding many undesirable side effects.

Title of Project:	New Cell Fusion Technique for Cancer Research
Principal Investigator:	Gerald Entine
Awardee Organization:	Biofusion-RMD 44 Hunt Street Watertown, Massachusetts 02172
Telephone Number:	(617) 926-1167

One of the most exciting approaches to the treatment of lymphocytic malignancies is the use of monoclonal anti-idiotypic antibodies directed against the surface immunoglobulin of malignant B lymphocytes. Such reagents combine with malignant lymphocytes but not with normal cells. In the most concrete success with this approach, a patient afflicted with diffuse, poorly differentiated lymphocytic lymphoma experienced a complete, extended remission induced by monoclonal anti-idiotypic antibody.

Although no further clinical trials have been reported, the approach seems so promising that Boston University Medical Center has initiated research into the production of anti-idiotypic antibodies for this purpose. The process of producing these antibodies consists of many steps, but one of these, the somatic cell hybridization of malignant B lymphocytes for isolation of malignant cell surface immunoglobulin, presents a particular problem because of the small number of lymphocyte cells available from all but extremely ill patients.

Recently a new fusion technique has been explored that uses electronic rather than chemical forces to induce fusion. This Electronic Cell Fusion Technique offers many attractive features, but the most critical is its ability to fuse very small numbers of cells with extremely high frequency. Initial fusion experiments on both mouse and human cells have been conducted with this technique and very promising results have been achieved.

Therefore, the objective of this research is to further investigate the Electronic Cell Fusion Technique and to collaborate with Boston University Medical Center in applying it to their project. By the conclusion of Phase II, the Electronic Cell Fusion Technique should be a widely used tool for cancer research and the work at University Medical Center should be accelerated.

Title of Project:	Evaluation of Reliability Growth Models
Principal Investigator:	Ilbok Lee
Awardee Organization:	Biostatistical Services, Inc. 29 Lee Terrace Short Hills, New Jersey 07078
Telephone Number:	(201) 467-8878

In cancer research, the statistical procedures that are developed are usually applied to ad hoc situations. For example, most statistical procedures in clinical trial evaluations focus on a particular treatment regimen that is effective against a specific type of cancer. On the other hand, reliability growth model methods can be used to analyze a sequence of clinical trials occurring over a period of years. Such an analysis can assess the growth in the success in treating a given cancer and predict success probabilities.

The specific purposes of this research project are: (1) to convert the data obtained from previous clinical trials on specified types of cancer or the data on both specificity and sensitivity in cancer screening tests to "successes" and "failures" required for analysis by reliability growth methodology, (2) to estimate the requisite model parameters and test the fit of the model to the data for the parametric class of models, (3) to assess the applicability of the nonparametric and Bayes procedures where the parametric techniques are not suitable, and (4) to extend existing models to account for such factors as clinical trials lasting for different lengths of time.

The principal research areas are: further development of parametric reliability growth models, extensions and modifications of the nonparametric models with an emphasis on Bayes and empirical Bayes techniques, and application and evaluation of existing and modified reliability growth models to assess clinical trial methodology and cancer screening procedures.

Methods developed in the research project will provide invaluable tools for assessing and, in some instances, predicting patterns of response in several areas of cancer research, that is, assessing changes in response rates in cancer clinical trials and assessing changes in sensitivity and specificity in cancer screening procedures. The evaluation of different screening procedures will be invaluable in setting policy on the various screening procedures.

Title of Project:	Luciferase-Antibody Conjugates as Immune Reagents
Principal Investigator:	Jill D. Fabricant
Awardee Organization:	Biosyne Corporation 2210 Maroneal, Suite 302 Houston, Texas 77030
Telephone Number:	(713) 432-1183

This project is developing bioluminescent reagents composed of firefly or bacterial luciferase convalently linked to specific binding proteins (SBP) such as monoclonal antibodies, polyclonal antibodies, lectins, and Protein A. These conjugates will be evaluated as reagents in luminescent immune assays (LIA) and as immunoluminescent stains (ILS). Proposed applications include the identification and assay of macromolecular antigens, small molecules such as drugs or hormones, cell labeling for flow cytometry/cell sorting, and the localization and visualization of antigens separated by electrophoresis.

Title of Project:	Preparation of Normal and Heritable Disease DNAs
Principal Investigator:	Lorraine H. Toji
Awardee Organization:	CytoTech International Inc. c/o AGH & R One Centennial Square Haddonfield, New Jersey 08033
Telephone Number:	(609) 966-7377

This pilot study is determining the marketability of DNA isolated from normal and heritable disease cell cultures, with the long-range goal of facilitating diagnosis of genetic diseases. If there is sufficient interest, the DNA isolation project will be expanded to include a larger fraction of the more than 3,000 heritable diseases.

Title of Project: Identification of Leukemia Associated Protein Antigens

Principal Investigator: Donald W. Bowden

Awardee Organization: Collaborative Research, Inc.
128 Spring Street
Lexington, Massachusetts 02173

Telephone Number: (617) 861-9700 extension 136

A methodology is being developed by which the genes coding for disease-specific antigens can be rapidly cloned using recombinant DNA techniques. The system lends itself to high-level expression of these antigens as hybrid proteins, which facilitates production of antibodies to the antigens. With both antigens and antibodies, immunodiagnostic tests can be produced for detection of these antigens in clinical samples. This system, encompassing recombinant DNA and immunodiagnostic techniques, can potentially discover large numbers of disease-specific antigens. A spectrum of antigens specific for one disease, and tests for them, could have considerable diagnostic and therapeutic value.

A cDNA library is being constructed from an established human leukemia cell line such as acute lymphoblastic leukemia (ALL). Clones carrying leukemia-specific sequences will be identified by differential screening with probes from normal leukocyte cDNA and probes from ALL cell line-derived cDNA. Cloning will be into the gtll expression vector. Clones carrying leukemia-specific DNA can be induced, which, with the gtll system, will lead to expression of substantial amounts of the antigen fused to -galactosidase (hybrid proteins). Because of their large size, the proteins can easily be purified and used to raise specific antisera.

Phase II will characterize the cloned, expressed antigens and their cognate antibodies. With the specific antisera, histological and immunological tests will be carried out to identify those antigens specific for the ALL cell line. In addition, other cell lines, including different established leukemia cell lines, will be tested for the presence of these antigens. Simultaneously diagnostic tests will be developed for these antigens, with the goal of using them for clinical diagnostic research.

The use of recombinant DNA techniques gives this methodology the power to find substantial numbers of as yet unidentified leukemia-associated antigens. This could lead to discovery of antigens useful in early diagnosis and treatment of a specific leukemia, and has the potential of discovering one or more antigens specific for more than one leukemia. This general methodology could be applied to the study of any specific disease.

Title of Project:	Thermographic Cancer Detection System for Home Use
Principal Investigator:	Satyanarayana Gupta
Awardee Organization:	CST, Inc. Post Office Box 7342 New Orleans, Louisiana 70186-7342
Telephone Number:	(504) 241-8011

This project is developing a novel thermographic cancer detection system for home use.

The basic underlying principle deals with microcapsules of temperature-sensitive liquid crystalline materials in polymeric shells as a free-flowing powder. These capsules, when applied to the skin of patients, will provide a visual thermographic scan to detect abnormal skin temperatures, which generally are due to abnormal tissues under the skin. This examination can be performed by the patient at home. The development of such a system will be particularly useful to detect breast cancer in women.

In Phase I of the program, materials that exhibit liquid crystalline characteristics between 32-36° centigrade will be identified from literature review. The physical and chemical properties of liquid crystalline materials suitable for thermographic applications will be determined from literature review and experimentation. A review of the properties will determine the process to develop capsules of about 50 micron size to be applied to the skin by a spray using compressed air. The capsules will be developed, characterized, and optimized for the application. Tests will be performed to prove their feasibility for thermographic applications.

Title of Project:	An Ultrasound Concentric Sector Biopsy Probe
Principal Investigator:	Terrance Matzuk
Awardee Organization:	Dymax Corporation 136 Gamma Drive Pittsburgh, Pennsylvania 15238
Telephone Number:	(412) 963-6884

The objective of this project is to develop an extremely compact ultrasound concentric sector biopsy imaging transducer and signal-processing subsystem having the capability of imaging the entire path of a biopsy needle in the plane of view, so that a brain tumor can be seen and biopsied through a single burr hole with the safeguards of image markers. Such a compact probe provides high resolution sector image through a small (1.5 centimeter) diameter acoustical window and a central needle access hole. Signal-processing electronics, drive control electronics, and marker electronics will be designed as a subsystem to optimize probe performance.

Benefits that will be derived from this research include:

1. Simultaneous visualization and penetration of the anatomical region to be biopsied or aspirated with the needle trajectory always within the field of view.

2. Small contact area for visualization and biopsy for difficult applications (for example, neurosurgery).

3. Improved safeguards and accuracy in biopsy procedures.

4. Reduction in medical liability resulting from invasive procedures.

Title of Project:	**SAR Estimation of Carcinogenesis Bioassay Results**
Principal Investigator:	Kurt Enslein
Awardee Organization:	Health Designs, Inc. 183 Main Street East Rochester, New York 14604
Telephone Number:	(716) 546-1464

The objective of this research project is to develop structure-activity models of certain carcinogenesis bioassays. Through these models it will be possible to predict the probability of carcinogenicity of untested compounds. The application will be to those chemicals that have not and probably never will be tested, but are already in current commerce, as well as those being introduced who commerce at the rate of approximately 1,000 per year. Other applications exist at the developmental stage to enhance the safety of laboratory and production personnel, and to minimize the use of animals in research and testing. During Phase I the feasibility of this approach will be demonstrated. Phase II would see a refinement of the approach and its commercialization.

The methodology consists chiefly of collecting results of carcinogenesis bioassays, evaluating them critically, and modeling assembled data bases by means of conventional multivariate statistical methodology.

The technological innovations expected from this project are the ability to predict to a degree not before possible which chemicals are likely to be carcinogens on the basis of structure-activity equations. The commercial applications are to those compounds in the Toxic Substances Control Act inventory that have not been tested, to chemicals currently being developed, and as a tool in the inventory's software implementation.

Title of Project:	A Rapid In Vivo Prescreen for Hepatocarcinogens
Principal Investigator:	Ellen M. Essigmann
Awardee Organization:	HGPARS Pharmaceutical Laboratories, Inc. 763D Concord Avenue Cambridge, Massachusetts 02138
Telephone Number:	(617) 354-2800

The objective of this Phase I project is to conduct pilot studies toward development of a rapid, reliable, and sensitive in vivo assay for screening potential hepatocarcinogens. The research effort is designed to provide preliminary information on the feasibility of using the choline-deficient rat, a model for liver tumor promotion, for this purpose. To accomplish this goal, male weanling rats will be maintained on high-fat semisynthetic diets that vary in choline content. Rats will then be subjected to either acute or subacute intragastric dosing regimens with the vehicle, potent hepatocarcinogen (AFB_1) or phenobarbital, a noncarcinogenic stimulator of hepatocellular hypertrophy and hyperplasia. Selected histopathological histochemical, immunocytochemical, and blood serum parameters potentially useful in detecting or predicting neoplastic change will be evaluated over time.

Results will be analyzed for evidence of dietary and dosing regimen effects on type, incidence, rate of development, and persistence of liver lesions. Data interpretation will allow determination of whether the choline-deficient rat model shows promise as a rapid carcinogen bioassay system. Phase II research will be directed toward determination of the sensitivity and specificity of the assay and toward further development for commercial exploitation.

Successful completion of this project will allow development of a commercially important bioassay system for use in contract toxicology companies and in industries that produce compounds requiring assessment for carcinogenicity.

Title of Project:	Human Prostate Carcinoma Specific Monoclonal Antibodies
Principal Investigator:	Paul J. Price
Awardee Organization:	Hybridoma Sciences, Inc. 4761 Hugh Howell Road, Suite D Atlanta, Georgia 30084
Telephone Number:	(404) 493-1902

The objective of this project is to develop monoclonal antibodies specific for prostate carcinoma antigens. Phase I is establishing and characterizing in vitro cell lines of human prostate cancer from biopsy specimens. These early passage cells will be used in Phase II as immunogens in the production of hybridomas.

As serum has been shown to stimulate fibroblastic growth, various hormones, growth factors, nutrients, and trace elements will be examined as substitutes for the serum supplement. Growth conditions that support the active proliferation of epithelial cells, prevent the deterioration of tumor cells, and suppress the growth of fibroblasts will be examined. Matrices to be examined include rat tail collagen, high density lipoprotein, and strips of collagen gels. Karyology, electron microscopy, growth in semisolid agar and nude mice, histology, production of prostatic acid phosphatase, and reaction with two monoclonal antibodies specific for prostatic antigens are being used to characterize the cell lines.

In Phase II, the monoclonal antibodies would be used (1) as a screening test for early diagnosis of prostate cancer by identifying prostate tumor antigens shed into the serum, (2) in imaging and therapy of metastatic prostate tumors, and (3) in identifying malignant cells in biopsy specimens as prostatic in origin.

Title of Project:	Development of a HAT-Sensitive Human Myeloma Cell Line
Principal Investigator:	Paul J. Price
Awardee Organization:	Hybridoma Sciences, Inc. 4761 Hugh Howell Road, Suite D Tucker, Georgia 30084
Telephone Number:	(404) 493-1902

The specific aims of this project are twofold. A hypoxanthine-aminopterin thymidine (HAT)-sensitive, nonimmunoglobulin secreting human myeloma cell line will be developed and characterized for specific application to human hybridoma production, and a tissue culture medium will be developed (not requiring conditioned medium or fetal bovine serum) to support the growth of this cell line. Both developments will make possible the use of human cell-derived monoclonal antibodies for cancer diagnosis and therapy. Monoclonal antibodies produced by the hybridoma technique of Kohler and Milstein have already been shown to have both diagnostic and therapeutic application. In tumor models, monoclonal antibodies conjugated to radionuclides, cytotoxic drugs or toxins, or even unconjugated monoclonal antibodies have demonstrated inhibition of tumor growth and in some cases regression of established tumors. However, due to the nonavailability of a nonsecretory, HAT-sensitive in vitro adapted human myeloma line for human-human fusions, mouse antibodies have been used for the most part. The multiple injection of foreign proteins such as mouse antibodies may result in an anaphylaxis, immune complex vasculitis, and/or the production of blocking antibodies in the patient. These problems would theoretically be reduced or eliminated in a human-human system.

HAT-sensitive mutants are being developed from a cell line, K737 (Lozzio), which was derived from the pleural effusion of a patient with multiple myeloma. The K737 cells will undergo 8-Azaguanine treatment in semisolid agar to develop the HAT-sensitive hypozanthine-phosphoribusyl-transferase deficient (HPRT-) mutants. During Phase II, the HAT-sensitive HPRT- mutants selected from Phase I will be further characterized as to growth properties, morphology, and fusion efficiency. The cell line will undergo further mutation in order to select for a HAT-sensitive HPRT- mutant that does not secrete immunoglobulin. Immunoglobulin levels will be tested by the principal investigator while karyology studies will be done by Dr. Lozzio. Also, during Phase I and II, a tissue culture medium based on a low-serum medium (HSI-LoSM) will be developed to grow the cells without conditioned medium and fetal bovine serum. The medium will be further tested against various other cell lines with particular emphasis on supporting the growth of established human and mouse hybridomas. This medium would allow for the production of monoclonal antibodies in culture without interference of fetal bovine serum proteins.

Title of Project:	In Vitro System for Isolating and Growing Cancer Cells
Principal Investigator:	Paul J. Price
Awardee Organization:	Hybridoma Sciences, Inc. 4690 Hammermill Road Atlanta, Georgia 30084
Telephone Number:	(404) 493-1902

The application of an in vitro model system for the isolation and propagation of cells having specific tumor properties is being demonstrated. The model system is also being used to test different media formulations for general applicability for growing carcinoma cells in vitro.

During Phase I, monoclonal antibodies already developed against serial cell lines of human prostatic carcinoma cells will be used to coat sterile polystyrene cell culture dishes. Fresh prostate tumor cells will be collected, minced, and mechanically or enzymatically separated and plated on specific antibody-coated, nonspecific antibody-coated, and control dishes. Cultures will be grown, propagated, and characterized as to origin and tumor genotype. Attempts will be made to grow the antibody-selected cultures in bulk. In parallel, monoclonal antibodies will be initiated against human breast and colon carcinoma cell lines to demonstrate in Phase II the utility and specificity of this in vitro model system.

Title of Project:	The Early Detection of Colorectal Cancer Using the ELISA
Principal Investigator:	Jerzy A. Georgiades
Awardee Organization:	Immuno Modulators Laboratories, Inc. 10511 Corporate Drive Stafford, Texas 77477
Telephone Number:	(713) 491-9595

The main objective of this research is to develop an improved diagnostic test for the early detection of occult hemoglobin in stools of patients. Colon and rectal cancer is the number two cancer killer in the United States. Most investigators feel that occult bleeding is the most frequent consequence and most predictive indicator of the presence of tumor. The high mortality rate of colorectal cancer makes the development of a diagnostic test for this cancer extremely important since early detection is associated with high cure rates. A number of tests have been developed to detect occult hemoglobin in stools. These include the dilute tincture of guaiac, saturated guaiac, Hemastat, and Hemoccult tests. In addition, the punch-disc radial immunodiffusion technique has been developed and has demonstrated greater sensitivity than the previously mentioned tests, as well as a degree of specificity not found in those tests.

A punch-disc enzyme-linked immunosorbent assay (ELISA) is being developed for the detection of occult hemoglobin in stools. The sensitivity of the assay should be clearly superior to that of existing tests. Because of its greater sensitivity, the punch-disc ELISA will allow detection of hemoglobin antigens at an earlier stage of colon cancer than the previously mentioned tests, leading to an increased survival rate. This newly developed punch-disc ELISA will be evaluated critically in terms of standardization, sensitivity, specificity, and reproducibility. These characteristics are essential to the quality control of the assay.

The findings in Phase I will be used to plan the demonstration in Phase II of the practical application of the punch-disc ELISA as a diagnostic technique for the early detection of colon cancer and other causes of alimentary tract bleeding. The detection of bleeding from noncancerous lesions could be an important aid in the cure rate of these lesions. The punch-disc ELISA is a specific, sensitive, accurate, and simple screening procedure that can be of significant value to practitioners, clinics, and laboratories as a quantitative assay capable of detecting hemoglobin antigen in the nannogram range. As a colorimetric assay, the ELISA offers the advantage of being adaptable to a simple and inexpensive office and home test.

Title of Project:	Mitotic Inhibitors from Human Colon Tumor Cell Lines
Principal Investigator:	John C. Houck
Awardee Organization:	Immunogenics Corporation 1000 Seneca Street Seattle, Washington 98101
Telephone Number:	(206) 583-6562

The objective of this project is to demonstrate that cultured human colon tumor cell lines produce autoinhibitory factors. The molecular weight of the inhibitory factor will be determined. Conditioned media will be collected from the SW-480 cell line under both serum-containing and serum-free conditions. The fractionation procedures have been designed to identify effectively possible high molecular weight and low molecular weight inhibitory factors. The specificity of the inhibitor will be determined by in vitro assays with a wide variety of normal and tumor cell lines.

The successful completion of Phase I will provide the data necessary for further development of autoinhibitory factors for human colon tumors. The molecular weight determined during Phase I will be used to design the necessary protocols for complete purification of the inhibitory factor and its eventual large-scale production. This production will be through either gene cloning, if the inhibitor is of high molecular weight, or by chemical synthesis, if the inhibitor is of low molecular weight. The successful development of such an inhibitor, specific for colon tumors, would be highly useful in the treatment of colon cancer, one of the predominant human cancers.

Title of Project:	Immunoadsorption Therapy for Kaposi's Sarcoma
Principal Investigator:	Joseph P. Balint, Jr.
Awardee Organization:	IMRE Corporation 130 Fifth Avenue North Seattle, Washington 98109
Telephone Number:	(206) 343-9550

Extracorporeal immunoadsorption to remove circulating immune complexes (CIC) and immunoglobulin G (IgG) results in complete regression of feline lymphosarcoma, clearance of persistent feline leukemia virus infection, and histologic changes associated with improvement in Kaposi's Sarcoma (KS) in man. This project is investigating the usefulness of an immunoadsorbent in removing CIC and IgG from the plasma of patients with KS and evaluating the clinical responses following this treatment. In addition, the physical proformance of the immunoadsorbent during plasma perfusion is being evaluated. These analyses will then enable the investigators to determine if there is a modification in the biologic response as a result of extracorporeal protein A immunoadsorption that is associated with clinical improvement and that will assist in the development of a safe, commercially available treatment device.

In order to remove CIC and IgG by extracorporeal immunoadsorption, protein A, which binds to the Fc of IgG, is covalently bound to a solid matrix. Columns are made using the immunoadsorbent. Plasma of patients with KS is perfused over the columns to remove CIC and IgG and the treated plasma is returned to the host. The CIC, IgG, and any other molecules bound to the column can then be eluted from the immunoadsorbent for characterization.

CIC are associated with several disease states including KS; therefore, if the removal of CIC from the plasma of KS patients during extracorporeal immunoadsorption can be demonstrated a wide range of treatment modulates may become available to clinicians. Immunoadsorption technology has been demonstrated to have potential therapeutic value in areas such as cancer and immune diseases, where the population base may be as large as 20 million patients or more.

These studies may result in the development of better clinical treatment products for cancer and immune diseases and also may provide basic information about the immunologic interaction between host and tumor.

Title of Project:	Immunoadsorption for Treatment of Malignancy
Principal Investigator:	Joseph P. Balint
Awardee Organization:	IMRE Corporation 130 Fifth Avenue North Seattle, Washington 98109
Telephone Number:	(206) 343-9550

Several recent reports suggest that extracorporeal perfusion of tumor-bearing plasma over protein A-containing substrates can result in objective tumor regression in the host. In this investigation, purified staphylococcal protein A is isolated, coupled to an inert biocompatible silica substrate, housed in a disposable cartridge, sterilized, and used to treat malignancy. A similar system has been used by the investigators and has resulted in objective tumor regressions in patients with breast adenocarcinoma.

This is a base research study to evaluate the tumor-bearing patient before and after extracorporeal treatment with specific aims toward the development of a safe and efficacious treatment unit and preliminary elucidation of possible mode(s) of action.

Patients being studied in this research project have stage II breast cancer and stage II melanoma. Ideal patients have local skin metastases or recurrence that can be directly observed for antitumor effects and biopsied. In the 6-month period covered by this project, it is estimated that 14 patients can be treated and studied employing extracorporeal protein A immunoadsorption.

The objectives of this study are to collect patient sera before and during extracorporeal immunoadsorption and to analyze the sera for quantitative changes in immunoglobulin levels, total hemolytic complement levels, circulating immune complexes, and tumor immunity (when appropriate). These immunologic parameters will be assessed in physical examinations, measurement of objective tumor (when appropriate), and x-rays of areas of tumor involvement. In addition, protein(s) bound to the protein A immunoadsorption will be analyzed for the presence of immunoglobulin, complement components, and immune complexes. These analyses will enable the investigators to determine if there is a modification in the biologic response as a result of extracorporeal protein A immunoadsorption that is associated with clinical improvement and that will assist in the development of a safe, commercially available treatment device.

Title of Project:	Development of TennaGen Enzyme Immunoassay
Principal Investigator:	Tommye A. Jordan
Awardee Organization:	JCL Clinical Research Corporation Route 46 Strawplains Pike Post Office Box 6275 Knoxville, Tennessee 37914
Telephone Number:	(615) 546-0654

The past decade has seen a great impetus in the search for tumor markers for the detection and management of cancer. This search has led to the discovery of several other carcinofetal proteins such as variants of carcinoembryonic antigen (CEA) and alpha fetoproteins. The tumor marker, Tennessee Antigen, appears to differ significantly from CEA in molecular weight, mobility in immunoelectrophoresis, carbohydrate residue contents, and most importantly, in antigenicity. The clinical evaluation of the antigen has been documented using a hemagglutination inhibition assay (TennaGen Assay). The statistical evaluation of 7,300 assays has been documented and appears to be very promising in colorectal and lung cancers.

The refinement of measurement of levels of Tennessee Antigen using the enzyme immunoassay methodology will increase the marker's use in monitoring clinical courses of treatment. The objective of this project is to use available Tennessee Antigen and antibody in the development of an enzyme immunoassay and to evaluate the sensitivity and value of the marker when using a more sensitive methodology than hemagglutination inhibition. The enzyme immunoassay will allow expansion of the scale of values so that one would have a greater differentiation between a negative range and a positive range compared to the range allowed by the hemagglutination inhibition assay. The readability of the assay by electronic apparatus will be more reliable and consistent among users than the hemagglutination inhibition assay, which relies on visual interpretation.

Title of Project:	Production of Monoclonal Antibodies to Tennessee Antigen
Principal Investigator:	John D. Jordan
Awardee Organization:	JCL Clinical Research Corporation Route 46, Strawplains Pike Post Office Box 6275 Knoxville, Tennessee 37914
Telephone Number:	(615) 546-0654

A new tumor-associated antigen, Tennessee Antigen (TAG), has been isolated from 95 percent of 154 primary human gastrointestinal tumors. Of 208 patients with colorectal carcinoma, 81 percent showed elevated leels of TAG in their serum. In this project, TAG is being isolated from extracts of adenocarcinoma of the human gastrointestinal tract. Monoclonal antibodies (MoAb) against TAG are being produced by the following procedure: Spleen cells from Balb/c mice immunized with TAG fuse with Sp 2/0-Ag 14 cells by means of 30 percent polyethylene glycol to produce hybridomas. Culture fluids from hybridoma are screened for antibodies by enzyme immunoassay. After identifying the cultures producing specific antibodies, the hybridoma cells are grown and cloned by limiting dilution in fluid phase. Lines producing MoAb are injected into Balb/c mice to produce MoAb-containing ascites fluid.

The MoAb will facilitate analysis of the structure and genetic origin of TAG. It can be used as part of a panel of MoAb to immunologically type the antigenic expression of colorectal carcinomas. Commercially, MoAb can be used for developing a sensitive radioimmunoassay for diagnosis of colorectal carcinomas. It may be useful in the treatment of human colorectal carcinomas.

Title of Project:	Real-Time Modeling and Control of Hyperthermia
Principal Investigator:	David M. Cooper
Awardee Organization:	K & C Medical University City Science Center 3624 Market Street Philadelphia, Pennsylvania 19104
Telephone Number:	(215) 233-4100 extension 230

Hyperthermia as a modality for the treatment of numerous types of cancers continues to show promise for clinical use, especially when used synergistically with low dosage x-rays. Methods of heat deposition include microwave, radio frequency, and ultrasound. To date, none is able to transmit the correct amount of heat to the tumor site with minimal interference to normal tissue in a controlled way. As a result, hyperthermia treatment of deep tumors has been largely ignored.

A scanning focused beam ultrasound hyperthermia delivery system has been developed for the treatment of deep tumors. This system features temperature monitoring within the tumor volume using thermocouples, flying-spot heating, and continuous recording of important parameters. Critical to the successful implementation of this system is the development of models that can provide real-time 3-D temperature profiles. These models must include temperature data at selected points, and provide for real-time feedback control by intensity modulation of the ultrasonic beam.

The method under development is to adopt simple models that retain the basic heat transfer processes and geometry and yet allow approximate techniques, such as the method of weighted residuals, to be applied for the solution. Considerable attention will be placed on handling blood flow and the power source term, which becomes temperature dependent by virtue of the feedback control. Progress to date shows the approach to be sound. The proposed research is crucial for the successful implementation of a sophisticated hyperthermia delivery system for clinical use. Simple 1-D models already developed by the researchers will be extended to 3-D and to geometries more representative of in vivo tumors. The new hyperthermia system will be clinically evaluated during Phase II.

Title of Project:	Low-Cost Medical Imaging
Principal Investigator:	Harry L. Loats
Awardee Organization:	Loats Associates, Inc. 24 Court Street Westminster, Maryland 21157
Telephone Number:	(301) 876-8055

The researchers are currently contracted to provide a microcomputer-based medical imaging system to the Johns Hopkins University Medical School to be used to analyze receptor autoradiograms. The system, consisting of hardware and software, quantifies optical density of photographic film to map neurotransmitter receptors in a variety of regions in rat, monkey, and human brains.

The purpose of this project is to extend the concept of low-cost imaging based on the prototype system to a user-friendly, microcomputer image system that could be used in any of a wide variety of neuroscience and other medical disciplines that use optical density variation.

Results of the prototype operation in an actual medical research environment will provide the basis from which the company will adapt programs and statistical techniques to enhance and automate the operator's tasks.

This project will provide a system of inexpensive image analysis directly adaptable to a majority of the current second generation microcomputers. The objective is a significant reduction in cost for a variety of medical imaging applications.

Title of Project:	Automated Instrument for Cell Sorting in Culture
Principal Investigator:	John C. Duffendack
Awardee Organization:	Meridian Instruments, Inc. 2310 Science Parkway Okemos, Michigan 48864
Telephone Number:	(517) 349-7200

The objective of this project is to design and construct a prototype instrument for cell selection and sorting. This device can be applied to cells in culture that are attached to a solid support and maintained under favorable growth conditions. This environment will be sustained within a novel incubation chamber, which provides flowing nutrient media and allows in situ analysis and sorting.

The instrument uses a laser-illuminated fluorescence microscope system, equipped with computer-controlled beam attenuation and two-dimensional stage movement. A dedicated microcomputer directs the sorting operations and provides graphic/tabular output of the acquired data.

The basis of cell selection is provided by fluorescent labeling of specific cellular components. After labeling, the instrument will examine the entire area of the growth plate and select cells based upon differential responses. Sorting then proceeds by either isolating the desired cells and their underlying support by a laser-inscribing action allowing physical separation, or by sparing the desired cells from a high-intensity laser beam that destroys all other cells.

Since most normal cell lines exhibit anchorage-dependent mechanisms to maintain cell function and differentiation, this development advances the art of cell sorting to include all types of cultured cells.

Title of Project:	A New Large-Scale Affinity Separation Technique
Principal Investigator:	Thomas W. Mix
Awardee Organization:	Merix Corporation 192 Worcester Street Wellesley, Massachusetts 02181
Telephone Number:	(617) 235-6630

In this project, the investigators are developing a new affinity adsorption and chromatography technique that offers great promise for commercial scale separations of biologically active materials such as interferon and growth hormone. The technique is based on attaching the affinity ligands to a hydrophobic liquid interface rather than to a solid support and is designated liquid-liquid affinity adsorption and chromatography.

In Phase I the feasibility and potential of emulsion affinity adsorption and of emulsion affinity chromatography will be demonstrated using a fluorocarbon as the hydrophobic liquid and bovine pancreatic alpha chymotrypsin enzyme as the model system. The purification and recovery achievable in single-stage emulsion affinity adsorption and purity, recovery, and throughput achievable with emulsion affinity chromatography will be determined. The results will indicate the relative emphasis that should be given these two approaches in Phase II.

Key benefits of the new technique result from: (1) its suitability for continuous countercurrent operation, (2) the simplification of product recovery resulting from the ability to coalesce the product emulsion and isolate the interfacial material, including the affinity ligand-product complex, with minimal washing and simplified elution, and (3) the reduction of steric effects.

Title of Project:	Magnetic Microsphere Depletion of T-Lymphocytes
Principal Investigator:	Kenneth J. Widder
Awardee Organization:	Molecular Biosystems, Inc. 11180-A Roselle Street San Diego, California 92121
Telephone Number:	(619) 452-0681

This research is directed toward developing means of using magnetic microspheres to rapidly and reliably separate target cells. Initially the target cells will be peripheral blood T-lymphocytes and the work will evaluate the ability to deplete this cell population. Later, the system will be applied to bone marrow in an attempt to eliminate graft versus host disease (GVHD). Removal of T-lymphocytes from donor marrow has been shown to greatly reduce or eliminate GVHD.

In Phase I of this project, the investigators are studying two different magnetic microspheres coupled to two different antibodies by various means for T-lymphocyte removal. T-lymphocyte removal, as judged by E-rosetting and fluorescent tagging, will indicate which microsphere-antibody coupling methods are the most efficient and cost-effective.

In Phase II the investigators will test the method(s) selected in Phase I for T-lymphocyte removal from normal donor marrow by biological assays and E-rosetting and fluorescent tagging. To assess marrow viability, the colony-forming ability of stem cells will be determined. The method(s) of choice will then be tested in patients. This research is designed to lead to a method that can be used in a clinical setting for preventing GVHD.

Title of Project:	Synthetic Hybridization Probes for Hepatitis B Virus
Principal Investigator:	Jerry L. Ruth
Awardee Organization:	Molecular Biosystems, Inc. 11180-A Roselle Street San Diego, California 92121
Telephone Number:	(619) 452-0681

The goal of this research is to develop synthetic DNA hybridization probes to detect individuals at risk for cancer. DNA hybridization has proven highly effective as a research diagnostic tool; however, conventional DNA hybridization probes are expensive to commercialize because they depend on enzymatically modified cloned DNA. Synthetic DNA's complementary to known sequences are relatively inexpensive to produce. These probes hybridize rapidly to specific sequences in DNA or RNA and are more sensitive to mutations and strain differences than cloned probes. Our goal is to develop an oligonucleotide-based test to detect hepatitis B virus (HBV), the integrated form of which is associated with hepatocellular carcinoma.

Phase I involves the synthesis and testing of normal and modified-oligonucleotides complementary to either the HBV surface antigen or core antigen genes. This phase of the project will compare the sensitivity and specificity of oligomer and cloned probes for filter-bound HBV sequences.

Phase II will refine the use of isotopic and nonisotopic probes to detect HBV in clinical samples in order to identify individuals at risk for cancer.

Once such probes are fully tested, clinical diagnostic probes for other sequences can be developed (for example, herpes virus, Epstein-Barr virus, and viral oncogenes).

Title of Project:	Prevention of Herpes Virus Diseases (Phase I: Molecular Biology)
Principal Investigator:	Yathirajulu M. Naidu
Awardee Organization:	Neogen Corporation 241 East Saginaw, Suite 517 East Lansing, Michigan 48823
Telephone Number:	(517) 332-8700

The objective of this project is to develop commercial applications of newer biotechnological methods for vaccine development to eliminate problems resulting from diseases caused by herpes virus. It is proposed to use the "Marek's Disease System" as an animal, virological, and molecular model for research on oncogenic diseases and other diseases caused by herpes viruses. Marek's disease is a neoplastic disease of chickens, resulting in significant economic losses. It is caused by a herpes virus (MDHV) but can be ameliorated by immunization with the nonpathogenic herpes virus of turkeys (HVT).

Phase I research is focusing on the prominent A antigens common to MDHV and HVT. Molecular characterization of the polypeptide of the MDHV-A and HVT-A glycoprotein antigens is being completed. Methods of analysis include size comparison on SDS-PAGE, staphylococcal V8 protease degradation, and tryptic peptide analyses. The cloned MDHV restriction DNA fragment(s) encoding the polypeptide(s) of the common A antigens by hybrid selection of mRNA, cell-free translation of the mRNA, and hybrid arrest of that translation will be identified. Results of Phase I should provide the genetic information encoding a well-characterized antigen in a cloned DNA form. Phase II would proceed with either expression of the genetic information in a bacterial expression vector, or chemical synthesis of immunogenic peptides.

Title of Project:	Real-Time, X-Ray-to-Coherent Optical Image Converter
Principal Investigator:	Robert F. Dillon
Awardee Organization:	Optron Systems, Inc. 118 Clark Street Newton Centre, Massachusetts 02159
Telephone Number:	(617) 965-3166

An x-ray-sensitive real-time spatial light modulator is proposed as a replacement for photographic film for several medical imaging applications--those in which time is of the essence, those that employ low x-ray energies (for example, oncology), and those used for the diagnosis of tissue movement (for example, action of the joints) in real time. The proposed device is a modified version of the Microchannel Spatial Light Modulator (MSLM). The MSLM employs a microchannel plate and a high-resistivity electro-optic crystal. The MCP converts x-ray images into electron images and deposits the electron image on the crystal. The resulting electric field in the crystal modulates the refractive index of the crystal and thereby alters the polarization of the readout optical beam. An optical intensity image is recovered by a polarizing analyser.

Phase I research is demonstrating the feasibility of x-ray image conversion, and characterizing the spatial resolution, framing speed, storage characteristics, and exposure sensitivity of the device. The Phase II research plan will be concerned with the problems of scaling the active area of the device up to about 6 inches in diameter. It is expected that the device will find widespread use in hospitals, on the battlefield, and in veterinary medicine.

Title of Project:	Phase Mixing in Countercurrent Chromatography
Principal Investigator:	Peter Carmeci
Awardee Organization:	P.C. Inc. 11805 Kim Place Potomac, Maryland 20854
Telephone Number:	(301) 299-9386

The multilayer coil separator is a new device that efficiently and rapidly separates chemical mixtures by partitioning between two immiscible liquids. One liquid is immobilized within a coiled column of tubing while the second liquid is pumped through the column. The technique is complementary to other chromatographic systems and has the advantage of employing no solid phase, thereby eliminating losses by adsorption. It is particularly useful for preparative purification of polar and labile substances such as natural products, amino acids, and proteins.

In Phase I, a modified multicoil separator is being constructed to permit visual and photographic studies of the mixing behavior of the immiscible liquids within the column. This information will be used to design improved columns for the separator. Other studies will determine the shortest column that can be used to reliably predict the attainable resolution of a mixture using a particular solvent system, greatly reducing the time needed to find an optimum solvent system. A novel multilayer trough column will be evaluated to determine if it provides increased resolving power as would be expected from present and photographic studies on columns investigated in Phase I. This phase of the project will include studies on new column designs and additional solvent systems, particularly some solvent systems that behave abnormally in multilayer coil separations. A major Phase II project will study the effect of temperature on solubility, partition coefficient, and phase retention. Phase II will achieve a significant goal of these studies, the construction of an apparatus operable at temperatures up to 50° Centigrade, which is expected to provide increased capacity and improved efficiency. In addition, a series of substances will be evaluated that will serve as standards to classify solvent systems used in countercurrent chromatography.

Title of Project:	A High-Resolution Separation System for Small Peptides
Principal Investigator:	Hisashi C. Iida
Awardee Organization:	Peptide Analysis Laboratory 5103 Acacia Avenue Bethesda, Maryland 20814
Telephone Number:	(301) 530-6709

A high resolution gel system is being developed for the analysis of small peptides in complex mixtures. The first dimension utilizes isoelectric focusing, containing immobile ampholites, glyoxylagarose, 6 Molar guanidine hydrochloride, and a fractionated triton X-100. The second dimension uses molecular weight separation with a linear pore gradient gel and cationic surfactant sodium cholate (SC), which forms a smaller micelle than SDS. The critical micelle concentration within SC is higher and easier to remove by washing.

Detection of the peptides will use an ultrasensitive silver stain, which is a modification of Merril's method. The fixation step, formerly done in a high concentration of acetic acid and alcohol, will be changed to 1.1 percent aqueous glutaraldehyde.

The above system will be distributed as laboratory trial kits as soon as they become available. It is anticipated that they will be used for biomedical research and in clinical diagnostic applications, as in the analysis of hormonal peptides in human spinal fluid or blood.

Title of Project:	Synchrotron Analysis of Trace Metals in Cancer
Principal Investigator:	Gilbert Davidson
Awardee Organization:	PhotoMetrics, Inc. 4 Arrow Drive Woburn, Massachusetts 01801
Telephone Number:	(617) 938-0300

The objective of this project is to evaluate the applicability of newly available ultra-high brightness x-ray source facilities (synchrotron light sources) to cancer-related problems in cell biology and morphology. In particular, potential applications in the areas of oncogenesis, early cancer diagnosis, and cancer therapy will be examined.

The synchrotron light source will allow imaging and analysis of trace metals in cells at concentration levels far below those previously visualized. It is expected that, using an x-ray microprobe beam line, trace metal concentrations at levels of interest will be measurable with spatial resolutions of approximately 1 micron. The extreme brightness (intensity per unit solid angle) of the synchrotron light source allows effective tuning of the energy of x-rays striking the sample. By this source energy selection, one can maximize fluorescence efficiencies for the trace metals, while minimizing background interferences.

Among applications of the analytical technique to be examined in Phase I are oncogenesis associated with metal toxicity, lymphocyte ferritin analysis in the early diagnosis of breast cancer, and platinum and other metal complexes used in cancer therapy. Phase I will define the application that has greatest potential and will include feasibility measurements on samples using an electron microprobe facility, with followup preliminary investigations at the Cornell synchrotron x-ray facility (CHESS). Phase II will provide complete experimental verification of one or more of these applications at one of the available synchrotron x-ray source facilities. The Phase III program will include the offering of this commercial synchrotron x-ray analytical service.

Title of Project:	Metabolic Feedback to Nutritional Support
Principal Investigator:	John A. Sargent
Awardee Organization:	Quantitative Medical Systems, Inc. 5901 Christie Avenue, Suite 201 Emeryville, California 94608
Telephone Number:	(415) 654-9200

The long-term objective of this project is to develop a product to provide a physician, who is prescribing nutritional support to critically ill patients, with a daily assessment of the metabolic response of patients to prescriptions. In particular, the first aim of this project is to demonstrate that net protein catabolism (PCR) can be calculated from blood urea nitrogen (BUN) and serum creatinine, thereby avoiding technical problems associated with daily urine collections. The second aim is to develop computer software that will relate the measured clinical and metabolic responses observed in patients and visually display this information for the physician prescribing nutritional support. The third aim is to demonstrate that a daily review of the metabolic response of patients to nutritional support will optimize the consumption of parenteral solutions and improve the quality of patient care.

These goals will be achieved by measuring protein balances (urine collections, intakes, losses, and change in body accumulation of urea) on nutritionally supported patients to validate protein balance estimates. These estimates use a single pool mathematical model of urea nitrogen, BUN, and serum creatinine to calculate renal clearance, rates of urea production, and PCR. This model has been validated in renal patients. Also proposed is a use analysis of parenteral solutions, and prescription of nutritional assessment by determining pharmacy disbursements and reviewing patient charts.

It is anticipated that good correlation between estimated and measured protein balances will result and that these data, when available to the physician, will improve the nutritional prescription by the way the patient responds to it.

The results of Phase I will provide the criteria for designing commercial software during Phase II. This software will calculate the daily assessment of metabolic response and will be designed for use on the microcomputers currently found in hospital intensive care wards.

Title of Project:	Systems for Hyperthermic Cancer Treatment
Principal Investigator:	E. Burnell Hranitzky
Awardee Organization:	Radiation Associates, Inc. 1906 Marlberry Houston, Texas 77084
Telephone Number:	(713) 757-7593

The objective of this project is the commercial development of systems for application to human cancer treatment with locoregional hyperthermia. The scope of the research includes the design of ultrasonic and magnetic induction devices (applicators) in order to determine feasibility and cost estimates for Phase II development of prototypes. In addition to the research into the design of the energy deposition applicators, a multifunction microprocessor system will be designed to control the function of the above applicators as well as interfaces to interstitially implanted electrodes also used for tumor temperature elevation. The latter type of energy deposition is given lower priority because it is an invasive procedure usually requiring surgical intervention, whereas the other methods are noninvasive. The multifunction controller will optimize the operation of the applicators, control tumor temperature, and function as the temperature measuring system. This latter system will have serial communications links to the controller as well as standalone capabilities and the capability to yield artifact free data in high radio frequency fields without the problem of field perturbation.

Title of Project:	Research on a Micro-GCMS for Biomedical Applications
Principal Investigator:	Russell C. Drew
Awardee Organization:	Viking Instruments Corporation 701 Clear Spring Road Great Falls, Virginia 22066
Telephone Number:	(703) 430-1515

The objective of the research in Phase I is to establish the feasibility of producing a small, lightweight, man-portable gas chromatograph-mass spectrometer (GCMS) that is capable of performing in-situ analyses of unknown compounds of biomedical interest. The design of the proposed instrument is based upon a miniaturized GCMS developed for the NASA Mars Lander program. The rugged design, stability, and highly automated operation of this instrument are well suited to a portable, terrestrial GCMS instrument that can be used for biomedical investigations, including field testing in emergency situations or under other circumstances where in situ analyses are necessary or desired. In this Phase I research, the basic design, which is now in a breadboard configuration, will be adapted to the special requirements of biomedical testing. This will incorporate an electro-optical ion detector (EOID) for increased sensitivity and selected ion monitoring as well as flexible ionization (currently electron impact ionization is used), simplified sample introduction into the GCMS system, and computer-aided identification of mass spectra.

Title of Project:	Teleradiology Diagnostic Imaging Pacs
Principal Investigator:	Thomas W. Doak
Awardee Organization:	Ratel-Medical Imaging Labs 911 Dell Avenue Campbell, California 95008
Telephone Number:	(408) 370-1010

This project deals with the development, initial testing, and evaluation of medical imaging systems, subsystems, and intrinsic hardware and software. It is concerned with teleradiology, which is the transmission of x-ray images using ordinary telephone lines or other electronic transmission media. Its intended use is to send these x-ray images from remote geographic areas to centrally located facilities where radiologists are available, so timely readings can be obtained. Diagnostic image assessment is a major research component because transmitted images must be sufficiently faithful to the original radiograph to support normal radiological practice at remote facilities.

Human reaction research is important because a "system" has human beings at both ends. If professional acceptance is lacking, the system will not work regardless of how well the equipment works. The ability to store images efficiently and economically and to retrieve them quickly enough for professionals to accept the system and use it is a critical feature. Examining these problems makes it clear there are five system parts: the communications network, the archiving medium, the data acquisition system, the display console, and the software (PACS).

Expected results of this Phase I project are the elucidation of a systems approach and the development, testing, and evaluation of equipment in Phase II to improve the delivery of health care in medically underserved areas by telecommunicating digital radiologic images. Experts agree that the economic advantages of replacing film-based radiography with digital systems could be enormous; one expert has calculated a $1 billion annual national saving.

Title of Project:	Dietary Mineral Assessment in Cancer Epidemiology
Principal Investigator:	Kirk K. Nielson
Awardee Organization:	Rogers and Associates Engineering Corporation 515 East 4500 South, Suite G-100 Salt Lake City, Utah 84107
Telephone Number:	(801) 263-1600

An increasingly pressing need is for dietary mineral assessments, especially as related to cancer epidemiology. The objective of this project is to establish a new analytical method for low-cost, nondestructive, multi-element analysis of solid and liquid foods. Specific aims and expected results are: validation of the new method for x-ray fluorescence (XRF) analysis of foods, measurement of feasibility for widespread applications to health-related analyses, and definition of new mineral data to directly support current epidemiological studies of colorectal cancer in Utah. The new technique uses the investigators' established mathematical method to automatically compute sample-specific calibrations using fluorescent x-ray intensities, backscatter intensities, and fundamental physics parameters. The method eliminates traditional needs for calibration and sample preparation to obviate matrix effects, thereby exploiting the advantages of rapid, low-cost, multielement XRF analysis with the accuracy and dependability required for food analysis. The validation, feasibility assessment, and measurements of data quality will allow prediction of the feasibility and expected results of an expanded Phase II study which will fill the present mineral data needs. It will also permit widespread commercial applications in industrial food testing, processing, quality control, and regulatory and labeling needs.

Title of Project:	Pattern Recognition for Chest Radiography
Principal Investigator:	Jack Sklansky
Awardee Organization:	Scanicon Corporation 720 Bison Avenue Newport Beach, California 92660
Telephone Number:	(714) 644-2229

The technical and commercial feasibility of a system of interactive pattern recognition for the semiautomatic analysis of digitized chest radiographs is being evaluated. A preliminary design for such a system, exploiting a parallel-pipeline multimicroprocessor architecture, is being developed in sufficient detail for a feasibility study. This design will include a capability for scanning, digitizing, analyzing, and displaying a wide variety of film radiographs at high speed and high resolution.

In this system the radiologist/user exercises control over computer algorithms that enhance the visibility of diagnostically significant details in the viewed radiograph and detect abnormalities based on the shape and textual features of the radiographic images of these abnormalities.

The system will increase the speed and accuracy of analyzing radiographs and will facilitate the introduction of numerical and graphical information into radiological reports. This design will have commercial applications as a subsystem of medical digital radiographic systems.

Title of Project:	Software Package for Survival Data Analysis
Principal Investigator:	Robert H. Mauritsen
Awardee Organization:	Statistics and Epidemiology Research Corporation 5225 16th Avenue, Northeast Seattle, Washington 98105
Telephone Number:	(206) 522-7372

The objective of this project is to develop a user-friendly software package for the statistical analysis of event time data ("survival" time data) in clinical trials and observational cohort studies. If successful, this effort will result in the availability of the major statistical methodologies for clinical trials in a form that is powerful and easy to use on a wide variety of mini and microcomputers.

Emphasized in the project is: (1) user-friendliness, (2) the observational prospective studies, and (3) portability among the new generation of powerful mini- and microcomputers. With these objectives, this software package would have applicability in both government-sponsored and privately-sponsored clinical trials and observational prospective studies.

To streamline this effort, it is proposed: (1) to use as a starting point, existing programs and subroutines, and (2) to design the software package in logically separate modules (analysis modules, data maintenance modules, and user interfact modules).

A potential commercial application of this proposed effort is the distribution of the software package, perhaps under a contractual arrangement with an appropriate distributor of scientific software. The demand for such a package is expected to be high becuse of the increasing use of the clinical trial and followup study methodology, notably in cancer research and in heart disease research, and the proliferation of a new generation of computers that are both powerful and inexpensive, thus bringing computing within reach of a broad spectrum of users, including clinicians, biostatisticians, and teachers.

Title of Project:	Insoluble Antineoplastic Particles for IV Injection
Principal Investigator:	Michael R. Violante
Awardee Organization:	Sterilization Technical Services, Inc. 7500 West Henrietta Road Rush, New York 14543
Telephone Number:	(716) 533-1672

Numerous compounds with known or suspected antineoplastic activity have been synthesized, which frequently are too insoluble or unstable in aqueous media for parenteral administration. Some of these compounds are not sufficiently soluble even with pH adjustment or minor solvent reformulations, and require a more complicated approach to their administration.

The objective of this project is to demonstrate that insoluble antineoplastic compounds can be prepared in the form of stable suspensions of particles of (1) 1 micron diameter, for intravenous administration and deposition in the reticuloendothelial system with subsequent slow solubilization and release to malignant tissues (primarily liver metastases and splenic lymphomas); and (2) 150-300 micron diameter, for intra-arterial delivery via selective catheterization of a tumor-feeding artery. These particles would partially embolize the vessel allowing subsequent slow solubilization and selective delivery of the chemotherapeutic agent directly to the malignant tissue.

The research is an extension of studies with radiopaque materials for tumor imaging. During these investigations, the following technical difficulties were resolved: (1) control of particle size distribution; (2) stabilization of suspensions in vitro and in vivo; and (3) selective delivery to liver and spleen (not bone marrow) following intravenous administration of particulate contrast material.

The methodology proposed in Phase I is analogous to the above-cited research and could, therefore, be initiated immediately. Specific goals of this project are: (1) determination of solubilities for selected compounds in physiological saline solution (PSS), plasma, and several organic solvents; (2) preparation of particles with desired size distributions; (3) determination of the tendency for particle aggregation in blood; and (4) evaluation of the use of albumin in preventing particle aggregation.

Important questions of efficacy and toxicity in experimental animals will be addressed in Phase II. The attainment of the project's goals could result in the therapeutic use of insoluble antineoplastic compounds that otherwise might not become available in the clinic. Also, the possibility of selective delivery and/or a depot mechanism for these compounds will be evaluated.

Title of Project:	Production of Antiserum Panel Against CSAp, COTA, and CEA
Principal Investigator:	Keshab D. Pant
Awardee Organization:	Summa Medical Corporation 4272 Balloon Park Road, Northeast Albuquerque, New Mexico 87109
Telephone Number:	(505) 345-8891

The overall objective of this project is to produce a panel of polyclonal (goat) antibodies against colorectal cancer markers such as colon-specific antigen protein (CSA_p), colon-ovary tumor antigen (COTA), and carcinoembryonic antigen (CEA) for the development of serodiagnostic and immunohistochemical reagents. These reagents will eventually be made into kits for commercial use. Phase I of this project is emphasizing only the immunohistochemical application of these reagents. The immunological approach to early detection and diagnosis of cancer relies on the premise that tumor-specific markers achieve circulation in the blood and are expressed both internally and on the surface of tumors in cancer patients. Immunodetection of these markers in our laboratory and others supports this premise.

In Phase I, polyclonal antibodies to CSA_p, COTA, and CEA are being produced; the specificity of these antibodies is ensured by a series of affinity adsorption procedures. Preliminary histological testing of this antibody panel will occur in New Mexico and in San Diego, California. In Phase II, production of monoclonal antibodies (murine/human) toward CSA_p, COTA, and CEA will begin and the $F(ab')_2$ fragments will be prepared under Food and Drug Administration Good Laboratory Practice/Good Manufacturing Practice (GLP/GMP) guidelines. While these later products may also prove useful as serodiagnostics and immunohistochemical reagents, their possible use in radioimmunoimaging will be evaluated.

Title of Project:	Design of a Compact Linac for Positron Tomography
Principal Investigator:	Marianne E. Hamm
Awardee Organization:	Technical Programming Services 315 Mission Drive Pleasanton, California 94566
Telephone Number:	(415) 462-4502

The goal of the research project is to provide the nuclear medicine community with a compact linear accelerator (linac) for the production of the principal short-lived radioisotopes used in positron emission tomography. The design of this linac will be based on exciting new technologies developed for a pion-generating linac (PIGMI) at the Los Alamos National Laboratory. These concepts will be combined with a revolutionary new commercial radio frequency power source to provide a clinically-based linac that will be more practical and economical than a compact cyclotron. The end point of the Phase I study will be a fully engineered design for a Phase II prototype, complete with established operating parameters and operating costs.

The Phase I design study will take advantage of Los Alamos' stated technology transfer policy to use the many advances made by the PIGMI program. Specifically, the various accelerator design computer codes developed at Los Alamos will be used to optimize the PIGMI linac design parameters for this project. All final system components will be fuliy documented in detailed drawings and a cost analysis for commercial production of the system will be provided.

Title of Project:	Development of Digital Radiation Detector/Monitor
Principal Investigator:	Philip A. de Langis
Awardee Organization:	Verité Technology Group 1614 West Anaheim Road Harbor City, California 90710
Telephone Number:	(213) 325-0200

The primary objective of this project is the development, testing, and evaluation of a small, low-cost device providing an accurate method of radiation detection and monitoring. This device would be worn by personnel working in radiation-exposed environments.

In general, the new device would (1) give the wearer multiple readouts of overexposure and accumulated radiation over a period of time (up to 1 year); (2) incorporate at least two alarms, one warning the wearer of dangerous exposure level, the other warning of an excessive accumulation of radiation for the time period since resetting the device. The primary thrust of this innovative technology will be the use of an insulated gate field effect transistor (IGFET) as a radiation transducer, and its characteristic leakage current as a correlative measurement. Using state-of-the-art hospital equipment, x-ray radiation would be the sole testing mode in Phase I.

Title of Project:	Test Protocol Data Base for Cancer Chemoprevention
Principal Investigator:	Anthony Lee
Awardee Organization:	Technical Resources, Inc. 3202 Monroe Street Rockville, Maryland 20852
Telephone Number:	(301) 493-5300

The objectives of the project are: (1) to develop a pilot data base on cancer chemoprevention testing in experimental animals that may be used as a model for any future data base development efforts, and (2) to evaluate a select portion of the available literature on testing for cancer chemoprevention to identify and consider data elements relevant to the development of test protocols.

To accomplish the first objective, literature is being gathered on prospective chemopreventive agents including Vitamin A and its analogs, Vitamin C, Vitamin E, β-carotene, selenium and various trace metals, phenolic antioxidants, protease inhibitors, prostaglandin synthesis inhibitors, uric acid, and secondary plant constituents. The resultant compilation will be the first effort to prepare a consolidated animal experimental data base on the subject. Literature will be reviewed and relevant information extracted onto formatted worksheets. This data base will serve as a foundation for future expansion.

To accomplish the second objective, the data base will be examined for specific parameters. This analysis will facilitate the development of test protocols for chemopreventive agents establishing criteria for validated research results and the future implications for human treatment.

Cancer chemoprevention is one of the newest frontiers of science. Any advancement in the field promises to have major economic and commercial impacts on the drug industry, training and education of health personnel, scientific and diagnostic instrumentation, and the life insurance industry.

Title of Project:	**Thermal Labile Liposomes for Drug Delivery**
Principal Investigator:	**Ronald C. Gamble**
Awardee Organization:	**Vestar Research, Inc. 939 East Walnut Street Pasadena, California 91106**
Telephone Number:	**(213) 792-6101 extension 301**

The in vivo site-specific delivery of drugs can increase the therapeutic effectiveness of drugs while reducing nonspecific toxic effects. The use of thermolabile vesicles for the delivery of drugs to specific sites is a potentially potent method for improving the specificity of drug chemotherapy in cancer and other diseases.

Previous reports have demonstrated the validity of the approach as well as the ability to formulate vesicles with sharp (1-3°C) phase transitions. This project is attempting to optimize these formulations to produce the sharp phase transition in the range 38-40°C. This Phase I effort will also attempt to demonstrate that encapsulated material is rapidly released during the phase transition, and, in a preliminary manner, demonstrate that vesicle-encapsulated material is maintained in circulation for prolonged periods and released at sites of externally-induced hyperthermia.

In biomedical applications, thermolabile vesicle formulations can be used to deliver pharmaceuticals and chemotherapeutics to specific sites with reduced toxicity to other parts of the body.

Title of Project:	Liposomal Delivery of Antitumor Agents
Principal Investigator:	Richard T. Proffitt
Awardee Organization:	Vestar Research, Inc. 939 East Walnut Street Pasadena, California 91106
Telephone Number:	(213) 792-6101

Phospholipid vesicles have often been acclaimed for their potential as anticancer drug delivery agents. However, there is little experimental evidence that confirms that liposomes actually target chemotherapy to solid tumors. The overall goals of this project are: (1) to verify that small vesicles with compositions that are recognized for their stability can be loaded with selected antitumor drugs, (2) to prove that such drug-loaded liposomes can increase drug uptake in experimental tumors while decreasing the level of drug in critical normal tissues, and (3) to establish that such vesicle targeting of chemotherapy can increase antitumor efficacy while decreasing the toxic side effects.

During Phase I, vesicle formulations prepared from pure phospholipids and cholesterol will be loaded with doxorubicin, a drug with cardiotoxic side effects. Drug-loaded liposomes and unencapsulated doxorubicin will be injected intravenously into separate sets of mice bearing solid Lewis lung carcinoma tumors. At various times after injection, blood, tumor, and heart tissue will be removed and extracted with 10 molar urea, and the extract will be analyzed for doxorubicin. A high performance liquid chromatography apparatus with a sensitive fluorescence detector will be used to separate the parent drug from its metabolites. Quantitative data on the drug concentrations in each tissue will be obtained.

Based on previous results with vesicle-encapsulated radioisotope, tumor uptake of the vesicle-encapsulated drug will increase, compared to concentrations attained with free drug. A twofold or greater increase in tumor drug exposure is thought to have significant therapeutic implications. Thus, if such an increase is observed, Phase II of the project, testing toxicology and therapy of vesicle-encapsulated doxorubicin, will be initiated.

The recognition that only the smallest vesicles, which are stable to leakage of encapsulated material while circulating in the blood, are capable of tumor targeting may lead to a renewed interest in these entities. If favorable tumor targeting can be demonstrated, this approach could have widespread health benefits and commercial applications.

Title of Project:	Encapsulated Paramagnetic Ions to Enhance NMR Imaging
Principal Investigator:	Ronald C. Gamble
Awardee Organization:	Vestar Research, Inc. 939 East Walnut Street Pasadena, California 91106
Telephone Number:	(213) 792-6101 extension 301

Proton nuclear magnetic resonance (NMR) imaging is rapidly becoming a major diagnostic tool in health care. The technique offers high-resolution images with the use of ionizing radiation. Diagnostic capability can be enhanced with contrast agents such as paramagnetic ions, provided they are site-directed and show low toxicity. Phospholipid vesicles (liposomes) are small submicroscopic shell-like structures that can encapsulate and localize paramagnetic materials within certain tissues in the body.

The aim of this work is to determine the extent to which entrapped paramagnetic ions alter proton relaxation rates (related to image contrast) for tissue known to have marked uptake of vesicles. Of particular interest is the evaluation of certain vesicle formulations that have significant uptake by at least 10 murine tumor types. In some instances, as much as 15 percent of the total injected dose of radiolabeled vesicles has accumulated in the tumor.

If successful, the research offers a new opportunity for improving diagnostic specificity with NMR imaging. In addition to targeted or altered biodistribution, contrast agents in vesicles will very likely exhibit lower toxicity. These advantages coupled with the low risk to patients of NMR imaging represent a large and very useful commercial enterprise, fulfilling a long-standing need by radiologists.

Phase II Projects

Title of Project:	Minimal Dose Digital Breast Radiography
Principal Investigator:	Paul J. Bjorkholm
Awardee Organization:	American Science and Engineering, Inc. 955 Massachusetts Avenue Cambridge, Massachusetts 02139
Telephone Number:	(617) 868-3814

This project proposes to use a patented x-ray detection technique and patented and proprietary digital data-handling techniques to build an x-ray mammographic imaging system producing diagnostic images that match or exceed the information content of existing techniques with a radiation burden of approximately 30 milliroentgen skin entrance exposure. The system will be capable of imaging 10 line pairs per millimeter over the entire breast, visualizing a calcification that is 0.2 millimeter in diameter. In addition, the system will be able to differentiate smaller density fluctuations than any other x-ray system. A 2 millimeter tissue tumor inbedded in a 6 centimeter-thick breast will be imaged at a signal-to-noise ratio of 19 to 1.

Before Phase I, AS&E demonstrated a very high-resolution, high-efficiency, 1-inch long detector. During Phase I it was demonstrated that two modular detector elements can be overlapped easily without any noticeable gap. Phase II will extend this modular detector to 8 inches and couple it with high-speed data acquisition devices to produce a prototype instrument for phantom testing. The instrument will be tested at a clinical site (Massachusetts General Hospital) with human volunteers.

The success of this testing will lead directly to the establishment of efficacy testing and then to breast cancer screening centers throughout the country.

Title of Project:	Synthesis of Imagable Iodinated Estradiol
Principal Investigator:	Richard J. Baranczuk
Awardee Organization:	Biomedical Research Lab, Inc. 2200 Commerce Tower 911 Main Street Kansas City, Missouri 64106
Telephone Number:	(913) 341-3222

Breast cancer is the most common type of cancer among women. The proper staging of this cancer and the determination of the presence or absence of estrogen receptors play major roles in determining the course of treatment. Methods available for such staging and estrogen receptor identification require invasive techniques (such as surgical biopsy) and in vitro assays. External imaging of tumors and their metastases through a highly specific estrogen-receptor-binding agent containing a suitable radioisotope would be advantageous because of its potential simplicity, noninvasiveness, and speed.

The objectives of this Phase II project are to use the synthetic techniques developed during Phase I for the rapid synthesis of $16\text{-}^{123}\text{I}\text{-}17$ estradiol and its rapid purification, to fully investigate the in vitro and in vivo utility of this compound for imaging estrogen-receptor-positive breast tumors and metastases.

A further objective of Phase II is to develop a new synthesis of an iodinated progestational compound that will exhibit all of the physiologic properties of progesterone in order to use the compound both in in vitro assays and for imaging purposes.

Title of Project:	Cervical Cancer Detection and Screening
Principal Investigator:	James W. Bacus
Awardee Organization:	Cell Analysis Systems, Inc. 826 South Lincoln Avenue Hinsdale, Illinois 60521
Telephone Number:	(312) 226-5193

The objective of this research is to develop new and improved diagnostic instrumentation for cervical cancer detection and screening. This will include the design of a prototype of an interactive logic module, a packaged arrangement of microcomputer chips and erasable programmable read-only memory (EPROM) logic that is optimized under considerations of size, manufacturing costs, and processing speed to aid in the performance of slide screening. The potential commercial application of the research is in the area of clinical laboratory instrumentation and testing. The public health benefits include: (1) a potential increase in accuracy and reproducibility of the Pap test, (2) a possibility of standardization from one screening laboratory to another, and (3) the potential of a readily available test for the general public.

Title of Project:	Cell Growth Chambers for Chemotherapy Drug Screening
Principal Investigator:	Elton M. Tucker
Awardee Organization:	Device Labs, Inc. 1600 Providence Highway Walpole, Massachusetts 02081
Telephone Number:	(617) 668-7111

Routine organization of a chemotherapy program based on test responses of the patient's tumor cells to proposed drugs has not been possible due to the lack of a practical, reliable laboratory test to define the most effective drug against a specific tumor mass. Major drawbacks associated with in vitro assays for sensitivity of tumors to specific drugs include the uncertainty of end-point validity, the need for large tissue samples, cost, and the question of conversion of the drug to active moities by metabolic pathways or alteration of drug activity by binding to plasma protein.

The technical and practical basis for a reliable, routine assay method and system may be found in the growth of tumor cells in small-pore diffusion chambers. The chambers, when implanted in rats, contain the cells, protect them from the cellular immune mechanisms of the rat host, and accomodate in vivo drug exposure of the patient's cells to the proposed antineoplastic drugs.

In Phase I of the program the manufacturing technologies and methods have been developed to reliably produce sterile cell growth chambers that can be easily used. Phase II is organized to study the growth characteristics of human tumors in the chambers, to determine if fibroblast overgrowth is a problem, to evaluate drug access to chamber interior, and to develop an operating room kit for preparing the test specimen at the time of surgical removal.

The drug sensitivity test based on this cell culture system can be performed with the basic cell culture laboratory equipment and personnel and requires a small number of tumor cells for analysis.

Title of Project:	Microcarriers from Inorganic Materials
Principal Investigator:	William J. Hillegas
Awardee Organization:	KMS Fusion, Inc. Post Office Box 1567 Ann Arbor, Michigan 48106
Telephone Number:	(313) 769-8500

Microcarrier systems show great potential for the large-scale growth of cells and the production of their metabolic products. The long-term objective of this research is to develop an inorganic-based microcarrier for growing fastidious, anchorage-dependent cells.

Silicon-based glass microcarriers are being produced that are the appropriate size and density for evaluation in suspension cultures that approximate the scaleup conditions used in large-scale cell culturing operations. Glass microcarriers have the potential to be cost-effective in industrial systems because of their expected durability (that is, potential for reuse), compatibility with a wide variety of cells, ease of washing, sensitivity to protease-mediated release of cells, and nonabsorbent nature (that is, neither media, sera, nor product are retained to dilute or contaminate the system).

Specific aims of the project are to examine the growth of several types of industrially useful cells under cultivation protocols compatible with large fermenters, and to compare their ability to synthesize useful end products, including infectious virus and soluble metabolic products, to that of diethylaminoethyl (DEAE)-dextran microcarriers. The expected advantages of glass microcarriers, such as their reusability and high sensitivity to protease-mediated release of cells, will also be verified.

Title of Project: Mass Spectrometry-Cold Electron Emitter

Principal Investigator: Robert A. Young

Awardee Organization: Quantatec International, Inc.
9773 Variel Avenue
Chatsworth, California 91311

Telephone Number: (818) 709-2966

Electron sources employing vacuum ultraviolet radiation and nonreactive photocathodes to replace hot filaments for ion formation in both quadrupole and magnetic mass spectrometers will be designed, constructed, and tested on each type of instrument. New photocathodes will be developed and used. Operation of an ion source at pressures from 1 to 700 torr will be investigated so that electron attachment and ion exchange can be used to form ions for mass analysis. Prototype ion sources will be installed in quadrupole and magnetic mass spectrometers and evaluated. Final engineering design for use with a popular quadrupole and a popular magnetic mass spectrometer will be developed.

Title of Project: Digitization and Archiving of Medical Images

Principal Investigator: Eric R. Craine

Awardee Organization: Rimstar Systems
c/o E/ERG, Inc.
2030 East Speedway, Suite 214
Tucson, Arizona 85719

Telephone Number: (602) 327-6380

The purpose of this project is to continue research and development on a large-format, high-resolution, two-dimensional image digitizer that consists of many optically multiplexed charge-coupled device (CCD) arrays. The specific aim of this Phase II project is to construct and exhaustively test a prototype digitizer consisting of a 2400x2400 pixel, seamless array attained by optical multiplexing of a 3x3 array of 800x800 pixel CCD's. The long-term objective is to begin manufacture of this digitizer for a number of potential markets. This digitizer can significantly impact many areas of the health industry. It is an important advance in the realization of widespread Picture Archiving and Communications Systems (PACS), and may prove to be one of the most important input devices available for these systems. It has great potential as a medical research tool as well as more mundane functions in document and record storage. The technology is state-of-the-art and represents an exciting new innovation in this field. The technology has been clearly shown to be feasible and considerable commercial interest has already been exhibited.

Title of Project:	Radioimmunoamplification Reactions
Principal Investigator:	Buck A. Rhodes
Awardee Organization:	Summa Medical Corporation 4272 Balloon Park Road, Northeast Albuquerque, New Mexico 87109
Telephone Number:	(505) 345-8891

The objective of this project is to develop and obtain FDA approval for a new diagnostic imaging agent for colon cancer. The approach is to use a cocktail of nonlabeled fragments of various monoclonal antibodies, followed by a second antibody that has the radiolabel Tc99m. This double antibody technique has the possibility of overcoming problems encountered with the clinical use of radiolabeled antibodies, that is, heterogeneity of expression to tumor-associated antigens and low-target to nontarget ratios of radioactivity uptake by the tumors. The development work is being done in nude rats bearing human colon transplants. Pharmacokinetic studies and dose response studies of both the first and the second antibodies will be carried out. The double antibody method will be compared to the single antibody method.

Title of Project:	Labeled Amino Acids as Diagnostics: New Synthesis
Principal Investigator:	Sun-Shine Yuan
Awardee Organization:	Tracer Technologies, Inc. 225 Needham Street Newton, Massachusetts 02164
Telephone Number:	(617) 964-4800

The project is continuing studies to disseminate stable isotope technology, focusing specifically on a single, short route universally applicable to the inncorporation of any carbon or nitrogen isotope into the 1-carbon or alpha-nitrogen of amino acids. Although nonradioactively labeled, amino acids will be used in tracer imaging and loading studies to monitor the course of diseases affecting protein dynamics and to assess the efficacy of treatment through hyperalimentation, so far no cost effective, high-yield routes for the bulk synthesis of these tracer diagnostic substrates have been developed.

Thus, the goal is to install a broad, but versatile, technical manufacturing base bringing together the applications of organic, organometallic, and stable isotope chemistry techniques heretofore unavailable in the production of cost-effective tracers for metabolic profiling and imaging, either by mass spectral or in vivo nuclear magnetic resonance (NMR) methods.

Specifically, the proposed work will achieve reaction scales in the 100 to 1,000 gram range for the synthesis with stable isotopes of leucine, alanine, and phenylalanine. Also to be developed are comprehensive pilot routes for valine, tyrosine, threonine, glutamic acid, and lysine, while introducing a timely innovation: the direct induction of optical activity by means of chiral catalysts.

Title of Project:	Transbronchoscopic Radioisotope Therapy System
Principal Investigator:	David P. Colvin
Awardee Organization:	Triangle Research and Development Corporation Post Office Box 12696 Research Triangle Park, North Carolina 27709
Telephone Number:	(919) 467-2878

The objective of this project is to further refine and develop systems that will permit the transbronchoscopic measurement of bronchial lumen diameter and axial dimensions and subsequent bronchoscopic implantation and retrieval of a selected radioisotope capsule for localized radiotherapy of malignant lesions. Such a system of devices would not only permit an accurate determination of bronchial dimensions and lesion sizes, but would also result in the development of a series of rigid and flexible devices that could be used for a variety of applications, particularly low-level, long-term, localized radiotherapy to deep malignancies, without surgery. Although not designed for most cases, it is believed that such an endoscopically-introduced system would have application for the treatment of small lesions, inoperable recurring tumors, and palliation for airway maintenance.

During the Phase II program, further development of both lateral and axial measurement devices, together with both point source and distributed-line source radioisotopic capsule systems and a single seed implantation system will be fabricated and evaluated. Testing during the first year will be in the adult lung model and in experimental animals such as a dog, sheep, and baboon. Pending successful animal tests, clinical trials will be initiated during the second year.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Phase I Projects

Title of Project:	Pediatric Publications Project
Principal Investigator:	Ann Acton
Awardee Organization:	Acton Associates 103 North Horrell West Frankfort, Illinois 62896
Telephone Number:	(618) 937-6157

The long-term objective of the project is the development and marketing of children's publications, to be used by caregivers and parents in helping young people understand and deal with traumatic events.

Specifically, the project will produce books or booklets dealing with pediatric health care events (hospitalization, surgery, emergency room and doctor visits, medication) at several reading comprehension levels.

Phase I will include market research with pediatric caregivers to determine the need, preferred content, and potential market for such publications, as well as documentary research to determine the most effective methods of written and pictorial presentation.

If a need and a potential professional market are identified during Phase I, the initial research in Phase II will develop four prototype books, do test marketing, refine the product, and evaluate the potential for full commercial production and sales.

Title of Project:	Computerized Life Skills Aid for LD Students
Principal Investigator:	Henry L. Blakely
Awardee Organization:	Athena Group Data Systems 122 6th Street, Southeast Washington, D.C. 20003
Telephone Number:	(202) 785-4990

This project is developing an interactive, microcomputer/videodisk tool for teaching life skills to learning disabled (LD) high school students. Called the life skills system (LSS), it is an attempt to remedy secondary school curriculum deficiencies in training LD students to function independently.

The LSS is based on functional context training, and thus is a distinct departure from traditional methods of computer-assisted instruction. In functional context, experiences are recreated rather than merely described. With the LSS, students have an opportunity to choose responses to realistic simulations of everyday life, and the system will present them with the logical results of their choices, while simultaneously recording and evaluating their responses for later analysis.

The high pictorial quality of the videodisk, combined with the computer's capacity for tracking through the decision trees created by student responses and its ability to superimpose text and additional graphics on the video image, will allow true-to-life simulations and will encourage exploratory learning and accelerate social and personal development. The system will be designed in concert with specialists in the fields of learning disabilities, educational software systems, video media, educational systems distribution, and potential users. It will focus explicitly on the mainstreaming needs of public and private secondary educational institutions, and thus should have wide commercial applicability and acceptance.

Phase I is a feasibility and developmental study leading to the creation of the LSS in Phase II.

Title of Project:	Automated Fetal Monitoring Records Management System
Principal Investigator:	Howard M. Hochberg
Awardee Organization:	Biomedics Inc. Post Office Box 971 Mercer Island, Washington 98040
Telephone Number:	(206) 392-8391

The hardcopy fetal monitoring record (FMR) produced and annotated during labor contains the history of the labor and is part of the patient's record. The bulk and form of the FMR is unacceptable for the chart, the medical records system, or long-term retention, all of which are critical to patient management as well as documentation of care provided. Microfilming is expensive and time consuming, and must be carefully managed. An efficient and effective solution is to automatically capture the FMR data during labor in order to print a hardcopy of archival quality suitable for insertion into the chart. Machine review and storage are added benefits.

This project involves adding memory, processing, and printing to Biomedics' digital bedside obstetrical data system (FetaScan 1000). This system will print all annotated FMR's in chart-compatible form at any time. Phase I covers building, validating, and documenting a prototype system. Validation will include clinical acceptability of the reformatted and compressed data, video review features, and a machine-readable storage method.

Title of Project:	Development of a Once-Daily Contraceptive Skin Patch
Principal Investigator:	Elie S. Nuwayser
Awardee Organization:	Biotek, Inc. 21-C Olympia Avenue Woburn, Massachusetts 01801
Telephone Number:	(617) 938-0938

The overall objective of this research is to demonstrate the potential of the Derma-Patch Drug Delivery System developed for the transdermal delivery of therapeutic agents. The specific objective is to illustrate this potential by testing in living animals a DermaPatch delivering levonorgestrel and estradiol, which are two major birth control steroids.

The DermaPatch transdermal delivery system releases the drug from rate-controlling microparticles (microcapsules and/or microspheres) that are suspended in a dermatologically acceptable viscous liquid base. The microcapsules release the drug in zero order and maintain a thermodynamically stable liquid base. Release is controlled by microcapsule size and thickness of the capsule wall. The microcapsules also prevent dose dumping caused by accidental rupture of the membrane. Another important feature of the system is a macroporous membrane that delivers a thin liquid film of the vehicle to the surface of the skin to occlude the skin. The film forces hydration of the stratum corneum with water from the lower layers of the epidermis and accelerates the delivery of the steroids. Because of the intimate contact between the skin surface and the thermodynamically stable viscous liquid base, uniform delivery of the drug is ensured throughout the treatment period.

Preliminary in vitro studies with the DermaPatch demonstrated that the permeation of levonorgestrel and estradiol from the system is constant and sustained. Studies further demonstrated that the permeation rates of the DermaPatch in freshly excised mouse skin significantly exceed the minimum 30 micrograms per day contraceptive dose for levonorgestrel.

The initial objective is to obtain additional data in vitro and in vivo on levonorgestrel and estradiol permeation. This information could lead to the development of a DermaPatch that combines both hormones as a birth control method for once-daily application. A DermaPatch of levonorgestrel and natural estradiol will make an excellent alternative to oral contraceptives composed of a progestagen and the potentially hazardous synthetic, ethinyl estradiol.

The transdermal delivery of contraceptive steroids offers significant advantages for the user in terms of flexibility, reduced dosage, and reduced side effects.

Title of Project:	Interactive Learning: Children's Health Education Books
Principal Investigator:	Steven Bignell
Awardee Organization:	Keneko Communications, Inc. 1700 Mission Street, Suite 204 Santa Cruz, California 95060
Telephone Number:	(408) 429-9822

Recently, Bantam Books, Pocket Books, and Random House have each published an enormously popular series of children's books. In these books, the reader is cast as the central character in the story and is required to make a series of decisions. Each decision is represented as a dichotomy. The reader is directed to different pages in the book, depending on the decisions made, and thereby experiences a particular set of consequences as a result of the choices.

The publishers attribute the series' popularity to several factors. The stories actively engage the reader, are short (usually 10 to 12 pages) and fast-moving, and allow the reader to exercise some control over the outcome. According to teachers who have used these books to teach students to read, they are particularly helpful in stimulating the interest of male students and of students who have shown little interest and/or who have been slow in learning to read. These books have not, however, been used as vehicles to convey specific factual information.

Because the commercial success and the interest and acceptance of this reading format by pre- and early adolescents have been so clearly demonstrated, this project proposes to apply this innovative concept to the development of a series of health education books for pre- and early adolescents.

In Phase I, through formal and informal surveys of teachers, health educators, children's publishers, and writers, the investigators will determine the viability and marketability of this concept and identify two to three appropriate health topics. In addition, the investigators will assess the feasibility of this interactive reading format to accurately depict the probabilities of various health outcomes as they relate to individual behavioral choices.

If the viability and marketability of this concept are borne out in Phase I, Phase II would develop a parallel series of two to three health education books using both the interactive reading format and a straightforward format. Effectiveness of these two educational formats would be compared using a tightly controlled experiment design. Impact on cognitive and effective outcomes and behavioral intentions would be assessed via multiple measurement techniques and instruments.

Title of Project:	Computer Diagnosis and Remediation of Dyslexia
Principal Investigator:	Marion L. Meeks
Awardee Organization:	M.L. Meeks Associates 12 Stonehedge Road Lincoln, Massachusetts 01773
Telephone Number:	(617) 259-0278

This project is developing a computer-based system for the early detection and remediation of dyslexia. This system incorporates animated color graphics, digital audio recording, and a touch-sensitive display. A child using this system receives recorded verbal instructions while watching a video display and responds by touching various images on the screen.

In Phase I the investigators are developing a prototype system, programming the operating software, and preparing a simple demonstration procedure to test the acceptance of the system by children. Phase II will develop a series of test programs for diagnosing dyslexia and providing remediation. The performance of the test programs will be evaluated in Phase II by direct comparison with the methods used at the Cortical Function Laboratory, Massachusetts General Hospital, and the Carroll School for Dyslexic Children in Lincoln, Massachusetts. If the effectiveness of the computer techniques can be demonstrated, an enterprise to deliver these services on a large scale will be developed.

Title of Project:	Design and Implementation of Software for Real Time ^{31}P NMR Acquisition
Principal Investigator:	Roger W. Wheatley
Awardee Organization:	Phospho-Energetics, Inc. 3401 Market Street, Suite 320 Philadelphia, Pennsylvania 19104
Telephone Number:	(205) 387-4429

This project involves the design and implementation of a software program to provide automated real-time acquisition and analysis of in vivo 31 phosphorous nuclear magnetic resonance (NMR) from the brains of neonates. This will permit the prediction or identification of life-threatening hypoxia so as to minimize the possibility of organ- and brain-damaged infants.

It is expected that the new software in conjunction with the NRM-isolette combination currently under development will establish itself in the marketplace for protecting premature infants from organ-damaging hypoxia. This minimization of infant organ damage will decrease health care costs for brain-damaged infants to their parents and to the Federal government.

Title of Project:	Project Simu-Teach
Principal Investigator:	Daniel J. Macy
Awardee Organization:	Macy Research Associates Route 5, Box 122 Wills Point, Texas 75169
Telephone Number:	(214) 896-1904

Project Simu-Teach is developing an interactive videodisk training system for teachers and parents of mentally retarded/developmentally disabled children of age birth to 6 years. Teachers and parents will be able to simulate the teaching of a child or infant by selecting instructional procedures via a personal computer and watching the child's reaction through the video monitor. The interactive videodisk coupled with random access audio technology is in the forefront of communication technology, and the proposed simulated teaching is directly comparable to the simulated flight training received by airline pilots. Commercial application will provide Simu-Teach systems in universities, schools, service agencies, and individual homes.

During Phase I, the investigators are researching and developing a prototype system representing limited curricular content and using videotape in lieu of a videodisk. Phase I includes a survey of the rate of use and validity of early intervention curricula, design of branching sequences for typical curricular objectives, production of visual recordings and software, and pilot testing of the prototype system. The Phase II Simu-Teach system will be the first interactive videodisk application in the education of handicapped infants and children. Major health benefits will result from improved preparation of service professionals, greater on-the-job proficiency, and increased parent effectiveness in fostering development of the mentally retarded/developmentally disabled infant and child.

Title of Project:	Non-Invasive Detection of Apneas in the Newborn
Principal Investigator:	Herman L. Watson
Awardee Organization:	Respitrace Corporation 731 Saw Mill River Road Ardsley, New York 10502
Telephone Number:	(914) 693-9240

The breathing patterns of newborns may be interrupted by central apneas (complete cessation of respiratory efforts) or obstructive apneas (lack of ventilation due to upper airway obstruction while respiratory muscle contractions continue to take place). Such apneas are thought to play a major role in Sudden Infant Death Syndrome.

Although a variety of monitors are available to detect central apneas, none is sufficiently simple or reliable enough to detect obstructive apneas. Respiratory muscle efforts during obstructive apneas are best detected by changes of intrapleural pressure, but heretofore this required insertion of an esophageal balloon catheter, which is too invasive for long-term monitoring. Intrapleural pressure swings in the absence of airflow at the nose and mouth establish the diagnosis of obstructive apneas. External monitoring devices placed around the rib cage or abdomen are generally effective for detecting central apneas but mightly falsely record normal breathing during obstructive apnea.

During Phase I of this project, the investigators are developing effective hardware and software to accomplish the goal of designing a device that can detect both apneas. The investigators will deal with improving characteristics of the device and developing a nasal airflow monitoring system with suitable microprocessor system algorithms for respiratory monitoring in hospital and home environments.

In Phase II of this project, it is anticipated that field trials will further refine the methodology. The techniques are based upon transducer knowledge developed by researchers, along with an important discovery on the relationship of cranial bone movements to the respiratory cycle. Movements of cranial bones detected by surface-inductive plethysmography closely resemble intrapleural pressure swings in newborn puppies and lambs. The proto- type device has a low signal-to-noise ratio and an unacceptable oscillator module mass for newborn humans.

Title of Project:	Noninvasive Test for Pediatric Nutritional Assessment
Principal Investigator:	Alfred M. Ajami
Awardee Organization:	Tracer Technologies, Inc. 225 Needham Street Newton, Massachusetts 02164
Telephone Number:	(617) 964-4800

This project addresses the development of noninvasive methods for evaluating nutritional status and body composition in pediatric patients. The kinetics of $^{13}CO_2$ exhalation in breath are being examined after bolus administration of $NaH^{13}CO_3$ and then significant parameters from the time course of tracer disappearance are being calculated. After a fast exponential distribution, the disappearance of $^{13}CO_2$ from breath is biexponential over a 3-hour period, in keeping with the concept that tracer is cleared more rapidly from perfused, metabolically active viscera and more slowly from perfused muscle mass. Area and moment analysis of the decay coefficients and exponents is expected to quantify these comparments in the fasting state in such a way that interindividual variations in endogenous metabolic rate and in body composition (viscera versus muscle) may be measured quantitatively.

Thus, the goals are to develop and validate a breath test for nutritional assessment that can be used either by real-time monitoring with a metabolic cart for nonradioactive carbon isotope detection or by interval sampling procedures amenable to workup in the clinical laboratory. If successful, the approach will represent an innovation over existing methods by combining the measurement of caloric requirements in the same test that characterizes body composition.

Phase II Projects

Title of Project:	Research on Sound-Making Products for Infants
Principal Investigator:	DiAnne L. Grieser
Awardee Organization:	Babeco 3938 Corliss Avenue, North Seattle, Washington 98103
Telephone Number:	(206) 632-3817

Visual "mobiles" are attached to infants' cribs to provide visual stimulation. No devices currently on the market provide infants with complex and interesting auditory stimulation. Yet, studies show that very young infants have a keen sense of hearing and are capable of discriminating fine differences in complex sounds such as speech. More important, infants like listening to speech, particularly when it conforms to the kind of speech that is addressed to them by caretakers. The particular kind of speech has many special properties, and has been given the name "Motherese." Laboratory research indicates that infants prefer to listen to Motherese over the kind of speech addressed to adults.

Phase I research examined the feasibility of creating an "Auditory Mobile" for infants, a device that presents Motherese and other complex signals that mimic its salient acoustic characteristics to infants. Substantial progress was made toward establishing the technical feasibility and marketability of such a product. Moreover, a large toy company expressed a firm interest in the commercialization of the "Auditory Mobile" and two other inventions that stimulate the auditory sense—the "Sound Maker" and the "Sensory Jack." Phase II will (1) identify the parameters of the auditory signals that should be contained in these products, and (2) work on the technical solutions involving complex signal processing required by these devices.

Title of Project:	Application Development of Gossypol Monoclonal Antibodies
Principal Investigator:	Joseph Ke-Chou Chen
Awardee Organization:	Bioqual, Inc. 11 Taft Court Rockville, Maryland 20850
Telephone Number:	(301) 251-0633

Gossypol is a yellow pigment present in the pigment gland of cotton seed that has been the subject of worldwide interest as a male contraceptive. Phase I studies were directed toward the development and production of monoclonal antibodies to gossypol. Several clones were established that are producers of antibodies highly specific to gossypol.

Phase II addresses the more definitive analysis of these antibodies along with production of the most useful to levels suitable for practical application. Generally the techniques used in the production of monoclonal antibodies in Phase I will be used in the Phase II studies to produce additional antibodies, followed by careful detailed analysis stressing the use of a competitive inhibition enzyme-linked immunosorbent assay (ELISA) test to quantitate the gossypol levels. The goal is the development of a nonisotopic immunoassay test kit to quantitatively evaluate the presence of gossypol. This will be especially important in evaluating the deposition and distribution of gossypol in toxicological and pharmacokinetic studies.

Title of Project:	Cryoprocessing of Superovulated Prepubertal Hamster Ova
Principal Investigator:	Geroge Yerganian
Awardee Organization:	Cytogen Research and Development, Inc. 89 Bellevue Hill Road West Roxbury, Massachusetts 02132
Telephone Number:	(617) 325-7774

This project involves the cryoprocessing and performance testing of superovulated prepubertal female Syrian hamsters as a cost-effective source of quality-assured eggs to service the needs of research and diagnostic laboratories engaged in human fertility testing and future generation risk assessments. Scheduling superovulation to encourage normal egg maturation provides year-round yields of 40 to 70 eggs from 25- to 33-day-old females. In addition, the ill-defined effects of egg aging in vivo, which accompany current superovulation practices applied to the cycling (mature) female, are minimized or eliminated by these procedures.

Freezing-thawing protocols will be applied to extend the storage life of eggs in liquid nitrogen. The fluorescein diacetate (FDA) assay will be used to assess egg recovery after thawing. Comparative performances of fresh versus frozen eggs in the human fertility ("Humster") test, conducted locally and at independent participating laboratories, are planned. The submission of jointly-prepared manuscripts to peer reviewed journals will assist toward formulating the marketing strategy.

In addition, use of pre- versus postovulatory eggs for human sperm pronucleus karyotyping will determine if egg aging in vivo reflects negatively on this vital test. Attention will be given to pH, osmolality, and use of ultrapure water when formulating solutions and media.

Title of Project:	Motion Simulation Effectiveness on Colicky Infants
Principal Investigator:	Ruth A. Humphry
Awardee Organization:	Sweet Dreems, Inc. 5465 Blue Cloud Lane Westerville, Ohio 43081
Telephone Number:	(614) 891-3455

The long-term objective of this project is to finalize, following Phase I findings and through a well-designed Phase II research program, the testing and development of an innovative and highly marketable motion/vibration product that has been proven to soothe fussing and crying infants diagnosed as having colic. Colic prevalence estimates range from 9 to 23 percent of the 1- to 3-month-old population, with few effective treatments available.

The specific aims are to: (1) Demonstrate the optimal effectiveness of motion simulation (that is, simulation of car motion)/vibration in soothing colicky infants; and (2) optimize the technical aspects and commercial applications for existing prototypes/vibration ranges. The supplementary aim is to determine the possible synergistic effect of motion with auditory stimulation and isolate the latter's contribution.

The methodology in the first experiment, using 60 subjects, will be to test the effectiveness of motion simulation (and the supplementary aim) using a highly-structured procedure with a factorial design and time-sampled behavioral outcome measures of infant response.

The second experiment, using 40 subjects, will examine long-term effectiveness (permanency) of motion in a 23-day study with infant behavioral responses recorded by the mother while measuring parental stress associated with infant colic fussiness and prototype use.

Expected findings will derive effective marketing parameters for a product that will ease colic and incorporate the following benefits: Minimization of infant pain; drug use; child abuse; family stress; and pediatrician's time devoted to colic.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Phase I Projects

Title of Project:	A Periodontal Temperature Probe
Principal Investigator:	Robert T. Kung
Awardee Organizations:	Applied Biomedical Corporation 33 Cherry Hill Drive Danvers, Massachusetts 01923
Telephone Number:	(617) 777-5410

The objective of this effort is the development of a periodontal temperature probe with response time and sensitivity characteristics that can provide an objective and simple diagnostic technique in assessing periodontal disease. Studies have suggested that inflamed sulci are accompanied by elevated temperatures. Conventional indications, such as bleeding upon probing, suppuration, or gingival redness, are highly subjective diagnostics for the detection of diseases.

The temperature-sensing element of the proposed probe is imbedded in the probe tip. The tip shape and size are similar to conventional periodontal probes with Williams markings. The advantages of such a probe are (1) the concurrent measurement of sulcular temperature and attachment level, (2) the identical probe insertion technique used in conventional attachment level measurement, and (3) the rapidity in allowing for multiple-site evaluation of disease.

The key features of this probe, which allows faithful measurement of sulcular temperature, is the specially designed low thermal mass of the probe tip. This feature provides minimal thermal perturbation to the regional tissues, thus allowing for a measurement accuracy of better than 0.1° Centigrade and a response time of under 2 seconds.

The Phase I program concentrates on fabrication and in vitro testing of the probe for reproducibility, sensitivity, and response time. A preliminary in vivo study will be performed to relate temperature to periodontal disease. The Phase II program will be oriented toward the clinical validation of sulcular temperature changes accompanying disease.

Probes with such special features are not currently available to clinicians. The simplicity of the concept and the similarity in dimensions to a conventional periodontal probe will greatly enhance its marketability.

Title of Project:	Improved Dental Composite Filling Materials
Principal Investigator:	Ronald W. Gumbs
Awardee Organization:	Gumbs Associates, Inc. 26 Avenue B Newark, New Jersey 07114
Telephone Number:	(201) 824-5110

The objective is to develop improved composite filling materials suitable for permanently restoring posterior and anterior teeth. Two primary objectives are to increase the concentration of filler to 90 percent by weight and to maximize the adhesion between the resin and filler.

The approach entails coating each filler particle with a thin film of polymer to obtain optimum adhesion. The coating is also tailored to permit high filler loadings.

The plan is to evaluate intensively the composites to show that it is feasible to prepare improved dental composite restoratives with 90 percent quartz. The following properties of experimental composites will be measured: water absorption, setting time, compressive strength, thermal expansion, density, color stability, and translucency.

Phase II will optimize the process and demonstrate durability and permanence after conducting accelerated aging tests and measuring the resistance to wear and thermal cycling before clinical evaluations.

A composite with the durability of a silver amalgam is expected to result. Because of its esthetic advantage, this composite restorative material should capture a significant portion of the market for posterior teeth restorations.

Title of Project: Laser Velocimetry for Periodontal Disease

Principal Investigator: Guy F. Bogar

Awardee Organization: MEDPACIFIC Corporation
6701 Sixth Avenue South
Seattle, Washington 98108

Telephone Number: (206) 763-2170

This research is developing a periodontal probe using a Laser Doppler Velocimeter Capillary Perfusion Monitor to provide a quantitative means of relating periodontal disease to blood flow and perfusion in the pocket of the diseased gingiva. Current methods, such as measurements of pocket depth, attachment level, and evidence of bleeding on probing, are unreliable and not correlated strongly with disease. An urgent research need is for the development of more accurate and reliable methods of assessing periodontal disease. A noninvasive method that can be used to test the efficacy of experimental treatments in relatively short time intervals is highly desirable.

The Phase I effort is expected to result in a prototype noninvasive probe and preliminary data regarding ease of use and sensitivity, and preliminary data regarding ease of use and sensitivity, and preliminary numerical data on an animal model. The probe will be tested by a dental researcher who will assist in the evaluation and provide suggestions for improvements for Phase II.

The probe could be used by dental researchers and later by clinicians when the relationships between laser Doppler probe measurements and periodontal disease are established.

Title of Project: New Controlled Release Antibiotic Delivery Systems

Principal Investigator: Richard W. Baker

Awardee Organizations: Membrane Technology and Research, Inc.
1030 Hamilton Court
Menlo Park, California 94025

Telephone Number: (415) 328-2228

The development of a controlled release system to deliver antibiotic drugs to the periodontal pocket, which could result in improved treatment of periodontal disease, is underway.

The system consists of antibiotic-containing microparticles, 100 microns in diameter, formulated as a suspension in a carrier medium. One formulation, to be used in the dental office, is a paste. This paste would be placed in the periodontal pocket by the dentist, using a syringe and thin rubber tube. The microparticles in the paste would release the antibiotic for a 2- to 4-week period, after which residual paste would be removed or replaced with fresh material.

The second formulation would be applied by periodontal patients. The microparticles in this formulation would release the antibiotic for 1 to 3 days. These microparticles are formulated in a cream suspension to be rubbed over the gums daily by the patient. A fraction of the particles would lodge in the periodontal pocket or teeth crevices, and the remainder would be removed by a mouth rinse. Both formulations would control antibiotic release by slow diffusion through a suitable microparticle matrix polymer.

Phase II Project

Title of Project:	Evaluation of a New Automated Periodontal Probe
Principal Investigator:	Khushrod Captain
Awardee Organization:	Foster-Miller, Inc. 350 Second Avenue Waltham, Massachusetts 02254
Telephone Number:	(617) 890-3200

The purpose of this research is to conduct clinical and laboratory investigations leading to a new automated device for measuring periodontal pocket depth and attachment level. The design includes a constant adjustable probing force, automatic detection of the cementoenamel junction, and automatic recording of attachment level with at least 0.2 millimeters of accuracy. The probe is designed to be safe for human patients.

During Phase I, a prototype probe was developed, tested, and found to provide excellent performance on extracted teeth in vitro. Based upon the knowledge and experience gained from the prototype, a hand-held automated probe will be constructed and assessments of accuracy and repeatability will be made. Studies using two periodontally healthy animal models and two with moderate to severe alveolar bone loss will assess repeatability and accuracy of measurements in comparison to conventional methods of probing. Repeatability of automated measurements will also be compared to conventional measurements in 15 humans equally distributed among three groups as follows: (1) periodontally healthy, (2) mild to moderate bone loss, and (3) moderate to severe bone loss. Accuracy of measurement will be determined in animals by comparison with direct measurements of attachment level on teeth extracted after probing.

The resulting probe will be a valuable tool for any research or clinical application that requires monitoring of attachment level. An immediate need is seen for the instrument in dental research: design simplifications planned under Phase II are expected to bring the purchase cost down to a level acceptable to practicing dentists.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Phase I Projects

Title of Project: Commercial Application of Biodetoxification Assays

Principal Investigator: David A. Brown

Awardee Organization: Aquatic Terrestrial Research (ATR) Corporation
1230 West 2nd Street
Los Angeles, California 90026

Telephone Number: (213) 482-3196

This research is designed to make commercially available a contaminant-specific assay of toxicity based on the partitioning of individual contaminants between sites of detoxification and sites of toxic action within exposed organisms. Immediate aims of Phase I are to test established procedures thoroughly and to verify the protocol developed to collect, store, and process samples to produce test results that are properly resolved into their component parts (enzyme-containing (ENZ), metallothionein (MT), glutathione-containing (GSH) pools); are contaminant-free and conform to highest standards of quality-assay/quality-control (QA/QC); and determine health implications when detoxification capacity is surpassed, thus laying the basis for implications for exposed humans. The assay is based on gel filtration procedures to determine the partitioning of specific contaminants of low molecular weight GSH pools, medium molecular weight MT pools, and high molecular weight ENZ pools.

Because high levels of contaminants are found today in urban recreational lakes from which people catch and consume hundreds of tons of fish annually, it is critical that contaminant effects upon human health be determined accurately. Fish liver tissues will be analyzed for biodetoxification using atomic absorption spectrophotometry, gas chromatography, gel filtration techniques, and histopathology examinations. Phase II will establish an index of toxicity, assimilation capacities for detoxification systems, and a blood chemistry program for noninvasive animal and human detoxification tests. A highly accurate toxicity test that will enable a clear determination of what specific contaminants are causing toxic effects in a multicontaminant environment has a very high potential for commercial application.

Title of Project:	Rapid Diagnostic Test for Chlamydial Infections
Principal Investigator:	Peter Nash
Awardee Organization:	Bio-Metric Systems, Inc. 9932 West 74th Street Eden Prairie, Minnesota 55344
Telephone Number:	(612) 941-0080

The rapid increase in the number of Chlamydial infections and the severe complications associated with this disease in humans have made it imperative to detect these agents in body fluids. The unique life cycle and characteristics of Chlamydial agents present a significant health threat.

In Phase I, a qualitative method of detecting low numbers of Chlamydial trachomatis is being developed. This sensitive, rapid detector uses an enzyme immunoassay system that produces a colored spot on a filter paper in the presence of the agent. Antibodies specific for the genus type antigens are bound to small particles and to a readout enzyme. These antibodies are mixed with the sample/specimen containing the agent, then filtered out onto a paper disk. A substrate solution is applied and the enzyme produces a color on the paper if the agent is present.

This method is quick, sensitive, and lightweight. The feasibility of this detector system is expected to be demonstrated in Phase I. In Phase II, an assay system sensitive specifically to 10^3 or fewer particles of pathogenic Chlamydial agents in fewer than 60 minutes assay time is expected to be developed and optimized.

Title of Project:	Work Environment Illumination and Filtration System
Principal Investigator:	Dale A. Rempe
Awardee Organization:	Delta Systems 620 H Street Geneva, Nebraska 68361
Telephone Number:	(402) 759-3997

This project is intended to provide superior air filtration and illumination to exacting hand-held operations that generate dangerous respirable dust and/or smoke, and to manufacture and market the resulting system. This involves the design, testing, and construction of (1) a quiet, lightweight, multistage air filtration system consisting of electrostatic and foam media filters and (2) an illumination system whose spectrum range and intensity level maximize user efficiency and comfort. Lighting and filtering systems will be combined into a system that encourages using the lighting range and area to properly orient the filter for maximum effectiveness (eliminating contaminants at the source and before chance of inhalation).

Success in construction of a workable filter-light system is expected to lead in Phase II to design of a proper transport system that allows the user to reposition the system easily relative to the source of contaminants.

Title of Project:	Annular Brain SPECT Detector Using Digital Position Analysis
Principal Investigator:	Andrew P. Smith
Awardee Organization:	Digital Scintigraphics, Inc. 49 Fairmont Street Belmont, Massachusetts 02178
Telephone Number:	(617) 484-8342

This project is part of a program to develop a commercially viable single photon emission computed tomography (SPECT) camera employing, for the first time, only digital position analysis procedures. Current effort is based on the use of an annular crystal offering much higher sensitivity and higher fidelity than available instruments. Other characteristics, such as mechanical simplicity, high event rate, and autocalibration capabilities, promise a camera with significant advantages for clinical studies.

Phase I involves developing digital algorithms designed to optimize resolution and uniformity, finalizing the optimum crystal size and photomultiplier requirements for a clinical prototype, and developing computer-controlled calibration procedures. On completion of Phase I, the obtainable performance of the laboratory prototype and how various parameters affect the performance will be understood. Detailed knowledge of the tradeoffs involved will lead to Phase II, the construction of a clinical prototype superior to existing single photon emission computed tomography systems.

Title of Project:	**A Short-Term Teleost Assay System**
Principal Investigator:	**Paula Gregory**
Awardee Organization:	**Innovative Technology, Inc. Southern Station Box 10072 Hattiesburg, Mississippi 39406**
Telephone Number:	**(601) 266-4707**

The overall objective of this project is to develop a teleost fry explant procedure as a simple, sensitive, rapid method of evaluating aquatic pollutants. Phase I will determine the feasibility of such a system by evaluating the technique with a direct-acting procarcinogen (benzidine hydrochloride) and a mutagen (mitomycin C). Phase I experiments will use two teleost systems—the sheephead minnow (Cyprinodon variegatus) and the rainbow trout (Salmo gairdneri).

Exposed explants will be examined morphologically and cytogenically (that is, chromosome banding, sister-chromatid exchange) and evaluated for their ability to form colonies. In addition, the mixed function oxidized system of the explants will be evaluated. In Phase II, monoclonal antibodies that recognize all surface antigens of transferred cells will be produced. These antibodies will be used as reagents for early indications of cell transformations in the teleost explant system.

Title of Project:	Transcutaneous Blood Lead Screening
Principal Investigator:	Michael Hercher
Awardee Organization:	OPTRA, Inc. 1727 Revere Beach Parkway Everett, Massachusetts 02149
Telephone Number:	(617) 389-7711

The specific aim of this project is to demonstrate the feasibility of using a noninvasive device, a transcutaneous method, for screening children and adults for elevated blood lead levels. The instrument will: (1) provide for a rapid and inexpensive test, (2) eliminate the hazards and problems of blood sampling, and (3) undoubtedly increase volunteer participation in screening programs due to the instrument's portability and benign test protocol. All these factors will significantly contribute to local health boards' ability to achieve the Federal guidelines for lead testing set forth by the Centers for Disease Control. The instrument will supersede the conventional screening technique and provide an excellent commercial opportunity.

The instrument will use the well-established correlation between erythrocyte zinc protoporphyrin fluorescence and possible lead intoxication. The skin surface will be illuminated with blue-violet light, and protoporphyrin fluorescence will be detected in the red. A dynamic measure of the quantity of erythrocytes in the observation volume will be provided by other optical techniques. A model comparison study of this method with conventional lead screening techniques is being conducted in Phase I.

Title of Project:	Induction of Transfer Factor Production by Bovines
Principal Investigator:	Gregory B. Wilson
Awardee Organization:	Intron, Inc. 701 East Bay Street Charleston, South Carolina 29403
Telephone Number:	(803) 577-2931

The objective of this project is to develop, manufacture, and market a product line of antigen/organism-specific transfer factors (an immune potentiator). The products will have applications for immunoprophylaxis and immunotherapy of a wide variety of human veterinary diseases for which a strong dependency on the development cell-mediated immunity for host protection has been documented. To accomplish this objective, antigen/organism-specific transfer factors will be developed by immunizing pregnant dairy cows.

Scientists have demonstrated that cows with cellular immune responsiveness to certain micro-organisms will harbor transfer factors specific for these organisms in post parturition colostrum and milk. Colostrum potentially represents a rich source of inexpensive transfer factor. It is not known, however, when or by what route a cow must be immunized to induce the accumulation of a particular organism-specific transfer factor in colostrum.

Phase I research is addressing: (1) the immunization route to be used, and (2) the number of immunizations and their temporal relationship to parturition. In Phase II, the information obtained from Phase I will be employed to bulk-produce certain transfer factors in bovines. Double-blind clinical trials will document the efficiency of this immune potentiator in selected human and veterinary diseases that have a major socioeconomic impact.

Title of Project:	Sea Urchin Embryos as a Teratogen Prescreen
Principal Investigator:	Richard S. Caldwell
Awardee Organization:	Northwestern Aquatic Sciences, Inc. Yaquina Bay Road, Post Office Box 1437 Newport, Oregon 97365
Telephone Number:	(503) 265-7225

The goal of this project is to develop a reliable teratogen prescreen test employing embryos of the sea urchin Strongylocentrotus purpuratus. A sea urchin embryo screen would complement existing tests designed to make potential teratogens at a relatively low cost a priority. The approach involves testing for mortality and structural abnormalities induced by chemical exposure during the embryonic development of the larval organism. Administering the chemical in an identical manner to a later larval stage, the pluteus larva, would permit a direct comparison between the concentration of chemical causing teratogenic effects (in the embryo) associated with unique embryological processes, and the concentration resulting in frank toxicity to an organism (the pluteus larva) not undergoing tissue differentiation and organogenesis of larval structures and function.

Phase I studies are concentrating on protocol development, including the selection of effects criteria, and initial evaluation of the experimental design. A select series of teratogens and nonteratogens, about 20 compounds in all, will then be examined using the method, to evaluate its feasibility. If the Phase I studies are promising, Phase II will refine the protocol, substantially enlarge the documentation data base of chemicals tested, and attempt to incorporate automation into the test. A reliable test will have commercial potential as a teratogen test service, and possibly for the manufacture of a partially automated test system.

Title of Project: Automated In Vitro Cytotoxicity Measurement

Principal Investigator: Kathleen F. Mead

Awardee Organization: OPTRA, Inc.
1727 Revere Beach Parkway
Everett, Massachusetts 02149

Telephone Number: (617) 389-7711

This research is directed toward the development of instrumentation and methods that will provide a rapid, simple, standardized system for assessing in vitro cytotoxicological effects. Standardized systems are necessary if the significant economic and technical advantages of toxicity tests are to be realized.

In Phase I, optical measurement techniques are being developed to quantitate certain universal cellular responses to chemical injury. Analysis will be performed on cell monolayers in the tissue culture dish using laser or xenon illumination and sensitive photometric systems. Lethal and sublethal effects of chemical substances will be assessed by light scattering and fluorescent dye measurements. In this manner, all current laboratory cytotoxic parameters--cell viability, morphologic change, cell growth, and reproduction--can be obtained.

A measure of the basal metabolic activity of the cells is also anticipated as part of this system. Furthermore, with additional optional fluorescent techniques (such as enzymatic, immunologic, or histochemical), the potential exists for quantitating specialized cell function. A rapid quantitative assay for phagocytic activity is also possible using fluorescent particles.

This research will lead to a versatile, inexpensive, automated tool for the quantitative analysis of cell monolayers in culture. The potential market is very large since (1) all in vitro studies initially require optimization of growth conditions, and (2) commercial and research institutes investigating and applying cytotoxicity assays would benefit from the reproducibility such instrumentation would provide.

Phase II Project

Title of Project:	Rapid Identification of Mycoplasmas with Immunoenzymes
Principal Investigator:	Michael G. Gabridge
Awardee Organization:	Bionique Laboratories, Inc. RFD #1, Box 2, Bloomingdale Road Saranac Lake, New York 12983
Telephone Number:	(518) 891-2356

Current methods for identification of microbial isolates from clinical human and animal specimens are fairly slow and tedious. Fast and simplified assays for pathogenic isolates would allow more rapid initiation of appropriate therapy and epidemiological control. Phase I demonstrated with mycoplasmas the feasibility of using an antigen-antibody reaction that was unique in the manner in which microbial antigen was immobilized (on cellulose acetate strips) and tagged (with an enzyme marker, amplified by a biotin-avidin high avidity lattice reaction). Chromogenic product was quantitated with a novel videodensitometer.

Phase II expands the study to include other common bacterial pathogens (Streptococcus, Hemophilus, and Salmonella). Specificity and sensitivity will be increased by using monoclonal antibodies and by developing blocking steps to reduce the number of naturally occurring active biotin sites on the microbial cells. The blocking agents evaluated will be bovine serum albumin (0.1 percent and 1.0 percent), horse serum (0.1 percent and 1.0 percent), and each of these serums with an additional 100 microgram per milliliter purified avidin. The densitometer will be modified to include both ultraviolet and white light (plus colored filters) used in a transmitted mode and a reflected mode. Significant effort will be made to facilitate automated data analysis by processing the densitometric signal with an integrator/printer, an analog/digital converter, and a microcomputer. Prototypes of the improved protocol and densitometer (which also can be used for a wide variety of scanning functions such as electrophoresis gels and enzyme linked immunosorbent assay plates) will be ready for commercialization within 2 years, and will contribute directly to improved laboratory operations and patient care.

NATIONAL EYE INSTITUTE

Phase I Projects

Title of Project: A Device to Precisely Deliver Microsized Eye Drops

Principal Investigator: Jon C. Thorson

Awardee Organization: Alpha Group Systems
19712 MacArthur Boulevard
Irvine, California 92715

Telephone Number: (714) 955-1140

An eye drop delivery system whose desired features have been demonstrated by an operational model is being developed into a production prototype that can be manufactured as a finished product, excluding contents, for under $1.00. The device will deliver precise microliter amounts of medication directly to the cornea without requiring unusual head posturing or eyelid manipulation. It will require minimal patient dexterity. The device will be disposable and nonrefillable, and will maintain the sterility of its contents. A lower quantity of active ingredients should be required to provide the desired therapeutic effect, and nonpreserved agents should maintain their sterility, thus providing the opportunity to reduce side effects produced by overmedication or preservatives inherent in present drop delivery systems.

Title of Project: Low Cost OCR Reader for the Visually Impaired

Principal Investigator: John R. Brookes

Awardee Organization: Energy Materials Research Company
2547 Eighth Street
Berkeley, California 94710

Telephone Number: (415) 524-3955

A low-cost optical character recognition device is proposed as a peripheral for microcomputers. The device in conjunction with speech output will be a low-cost reading device that visually impaired individuals can afford. The development strategy will focus on a feasibility demonstration of a low-cost photodetector in conjunction with transportable "C" code. The wider commercial applications of this device for archival data entry are expected to provide commercial incentives to lower the price to visually impaired individuals. To this end, sources of private funds will be located.

Title of Project:	Dye-Enhanced Laser Hemostasis and Tumor Cell Killing
Principal Investigator:	Horace W. Furumoto
Awardee Organization:	Candela Corporation 96 South Avenue Natick, Massachusetts 01760
Telephone Number:	(617) 653-7373

The investigators in this project are developing lasers suitable for irradiating externally supplied chromo- phores (dyes) in tissue using selective photothermolysis. Selective photothermolysis allows precise target specificity in vivo by color selectivity. Spatial selectivity does not depend on focusing but on time resolution. Large tissue volumes can be treated simultaneously and nontarget tissue spared.

The lasers will be compatible with existing Food and Drug Administration-approved sterile dyes. Studies will be conducted on animals for the treatment of senile macular degeneration, hemostasis of gastrointestinal bleeding, and tumor cell killing by the irradiation of dyes conjugated to monoclonal antibodies. The lasers will emit in the near infrared and will have pulse durations corresponding to target size (submicroseconds for cells and milliseconds for vessels).

The emphasis will be on the treatment of senile macular degeneration, the leading cause of legal blindness in the United States. Most people with senile macular degeneration go blind because of choroidal neovascularization. Selective photothermolysis promises to be superior to existing photocoagulation techniques for treating senile macular degeneration.

If feasibility is proven on animals in Phase I, the treatment of human subjects will be the focus of Phase II. Phase III will result in a commercial product.

Title of Project: Behavioral Myopia Remission Using Biofeedback

Principal Investigator: Robert J. Randle, Jr.

Awardee Organization: Illiana Aviation Science
2090 Wyoming
Las Cruces, New Mexico 88001

Telephone Number: (505) 522-8402

Functional or behavioral myopia is a serious handicap in our society, characterized as it is by emphasis on educational pursuits with high visual workload. In industry, the increasing use of video terminals is exacerbating the problem. Behavioral myopia appears to develop through long-term deprivation of the far visual response brought about by overuse of the near response in conjunction with unrecognized internal stress. A progressive phenomenon, it appears to have strong emotional, personality, and stress components.

The goal of this research is to demonstrate that myopia remission may be attained through the use of auditory feedback of the ongoing accommodative state provided by an automatic, servo-controlled, infrared optometer. The strategy will be to bring into awareness the learned and habitual ciliary spasm by coupling the visual accommodation response from the optometer to a tone generator. This will provide an explicit indication of the current state of the focus response, of which the trainee is fully conscious. This research will provide a technological basis for defining a simpler, low-cost device for the visually handicapped.

Title of Project:	Clinical Eye Movement Analysis System
Principal Investigator:	Stefan T. Sitko
Awardee Organization:	Neuro Logic Systems 4414 Stewart Avenue Los Angeles, California 90066
Telephone Number:	(213) 390-4216

The objective of this project is to develop a dedicated clinical system for testing and analyzing ocular motility. Commercially, the goal is to produce a low-cost, user-friendly hardware/software package specifically designed to allow clinical personnel with no computer training to quantitatively analyze (online) the eye movements produced in patients during pursuit tracking, random saccade tests, caloric irrigation, optokinetic and positional nystagmus testing, and (optionally) rotatory tests of vestibular function. A central control/analysis unit will be developed using the latest microprocessor and memory technology, and programmed using proven software algorithms. A solid-state stimulator for smooth-pursuit and optokinetic testing will be developed as well as a solid-state thermal probe for caloric stimulation.

Phase I is intended to investigate a new means of monitoring eye movements using phase-sensitive detection of a high-frequency carrier signal impressed across the eye to measure impedance changes produced by eye movements. Lock-in amplifier and phase-locked loop technologies will be used to detect and process the phase-shift information. The success of this project would provide a new atraumatic means for monitoring eye movements, overcoming several major problems inherent in conventional electrooculography recordings.

Title of Project: Surface Modification of Gas Permeable Contact Lenses

Principal Investigator: Jeffrey E. Koziol

Awardee Organization: Plasma Tech Corporation
249 Sunset
Palatine, Illinois 60067

Telephone Number: (312) 397-3620

This research is designed to improve long-wear contact lenses so that they will not affect the cornea, and to reduce eye disease caused by wearing contact lenses. A lens will be produced that is highly oxygen permeable and yet has a surface that is wettable and resistant to deposits. A core of pure silicone with an ultrathin plasma polymer surface will be used. Silicone will provide a lens that is oxygen permeable, soft, and optically clear. A plasma polymer that is highly crosslinked, formed when methane gas is polymerized, can be deposited on the surface of silicone to form a barrier to tear film deposits and to make the surface wettable. Because the plasma polymer is thin, oxygen permeability will not be appreciably affected.

Phase I has two goals. The first is to establish the conditions of plasma polymerization that lead to the most crosslinked methane polymer and to establish a thickness of methane polymer that is most durable. The second is to improve the procedure of incorporating hydrophilic groups into the structure of methane. It is expected that Phase I will establish a technique to produce a plasma polymer 100-200 angstroms thick that is wettable and impermeable to tear film deposits. Using a simple gas such as methane to produce such a polymer can give easily reproducible results that can be repeated economically on a large scale.

Title of Project:	Research Related to Developing a Visual Testing Device
Principal Investigator:	Edward M. Brussell
Awardee Organization:	Q-T Products, Inc. Post Office Box 262 202-11 Jamaica Avenue Hollis, New York 11423
Telephone Number:	(212) 479-5858

Qualitative advances in computer technology have leveled off enough to justify development of a multiuser, multifunction, comprehensive visual testing instrument for ophthalmologists, visual scientists, and optometrists. Such a system could be developed with relative ease were it not for the industry standard refresh rate for generating video images. Unfortunately, 60 Hertz is too slow for creating the visual stimuli needed to assess temporal aspects of vision.

Cost-effective alternatives to the more obvious solutions that involve modifying or redesigning hardware are possible. They entail generating images that contain fewer lines, but that are painted at a faster rate. This solution, however, begs the empirical question of how a sacrifice of vertical resolution in a stimulus image will influence visual performance. Therefore, research is proposed to provide the data to answer this question. Specifically, the influence of the number of stimuli presented at one time (stimulus uncertainty) and the density of lit pixels per unit area of a stimulus image (spatial summation) on a temporal resolution task known as Multi-Flash Campimetry will be investigated.

Phase II Project

Title of Project: Noninvasive Detection of Glaucoma

Principal Investigator: John S. Scott

Awardee Organization: Rimstar Systems
c/o E/ERG, Inc.
2030 East Speedway, Suite 214
Tucson, Arizona 85719

Telephone Number: (602) 327-6380

The goal of this project is the development of a system for use by clinical ophthalmologists that will apply new technologies of image digitization and processing to the problems of early diagnosis of glaucoma and related optic nerve atrophy. Specifically, Phase II continues research and development of a prototype device that can be used to: (1) acquire high-resolution, high-precision digital images of the optic disc at very low light levels; (2) digitize for computer manipulation already existing fundus photographs; (3) automatically measure the two halves of a digitized stereo pair of fundus images to determine parallax; and (4) reduce the results of the measurement, through the latest in photogrammetric software, to produce quantitative maps of the "topography" of the cupping of the optic nerve head.

That these goals are achievable is demonstrated by the proof-of-principle work performed in Phase I. In Phase III the methodology will be refined to produce a compact, low-cost, user-friendly device capable of performing the above functions. It is widely recognized that accurate photogrammetric determinations are crucial in early detection of glaucoma.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Phase I Projects

Title of Project:	System for Automated Human Performance Measurement
Principal Investigator:	Dorothy E. Fletcher
Awardee Organization:	Ecosystems, Inc. University City Science Center 3624 Market Street Philadelphia, Pennsylvania 19104
Telephone Number:	(215) 382-6900

The objective of this project is to develop a low-cost, open-ended automated laboratory system for performance measurement of abilities that contribute to human mental, sensory, and psychomotor performance (online computer-controlled presentation of test stimuli, subject response direct to computer, scoring and statistical processing by computer). Specific aims include: (1) development of software for presentation of subject stimuli, involving graphics on a video display screen, (2) development of a structural housing and digital electronics for a subject display/response console, (3) selection and development of interface software for a system microcomputer, and (4) thorough test of hardware and software. Such a system could be used to test or investigate human responses and adaptations to drugs, toxic gases, hypoxic states, fatigue, mental disorders, and disease states.

Phase I involves prototype development (computer-generated test graphics and subject display/response console) and selection of the microcomputer. Phase II involves completion of the entire system prototype and thorough testing. Innovation involves potential for systematizing and making generally available many tests of human performance, with individual users able to develop their own tests or modify existing tests by changing software, not hardware. Commercial application potential extends to a wide range of users of human performance test devices.

Title of Project: Improved Procedure for Genetic Analysis

Principal Investigator: Robert G. Pergolizzi

Awardee Organization: Enzo Biochem, Inc.
325 Hudson Street
New York, New York 10013

Telephone Number: (212) 741-3838

In this project the investigators are developing sensitive, rapid, and easy-to-use methods for nonradioactive detection of DNA:DNA hybrids using biotin-labeled DNA probes. The approaches are directed toward incorporating a greatly increased number of biotin molecules into DNA molecules associated with the hybridizing probe. Since the enzymatic color producing detection of hybridizing sequences is dependent on detection of biotin, a marked increase in biotin molecules, that is, reporter molecules, associated with a hybridized probe should result in a marked increase in sensitivity.

One approach is a concept in which one biotinylated probe will suffice for the detection of any sequence cloned in the appropriate vector ("universal detection"). Another is to develop method(s) for the use of single-stranded-phage DNA probes labeled with biotin by primer extension.

Since sensitivity can also be increased by improvements in the biotin-detecting enzymatic color-producing component, methods are proposed to develop greater sensitivity for this component.

These procedures using Southern blot technology are being developed for direct examination of DNA for genetic analysis. The development of safe, sensitive, and easy-to-use Southern blot procedures will greatly extend the clinical use of genetic analysis.

Title of Project: Rapid Approaches for Production of Genomic DNA Probes

Principal Investigator: Kirk E. Fry

Awardee Organization: Gene Labs, Inc.
871 Industrial Road, Building J
San Carlos, California 94070

Telephone Number: (415) 594-1600

Current methods to isolate clusters of DNA fragments linked to a given marker are slow and cumbersome. Methods for in situ hybridization of unique copy gene sequences to human chromosomes are also difficult and at the limit of consistent reliability. This project is developing a series of steps that provide a more rapid approach for localizing given unique DNA fragments by in situ hybridization and also for chromosome walking procedures for DNA-spanning regions of the chromosome larger than may be propagated as an intact DNA piece in available vectors. These procedures are being applied to isolate a set of random DNA fragments that are evenly dispersed along the entirety of the human genome and to identify polymorphic fragments within this set so as to develop a universal set of probes for studying linkage of diseases of unknown etiology.

Title of Project: Preactivated Latices for Research and Diagnosis

Principal Investigator: Wolf Karo

Awardee Organization: Polysciences, Inc.
400 Valley Road
Warrington, Pennsylvania 18976

Telephone Number: (215) 343-6484

The objective of this project is the development of new functionalized polymer latices for separation and identification of clinically significant proteins. The investigators expect that they will improve the efficiency and specificity of binding of proteins (antigens, antibodies), thus allowing improved research and immunological test procedures and use of rare monoclonal antibodies not now possible with passive, nonspecific polystyrene latices that are now standard.

Specifically, a series of monodisperse, emulsion copolymers of methyl methacrylate with either glycidyl methacrylate, acrolein, or aziridinylethyl methacrylate are to be prepared. Problems of control of particle diameter, reactivity to proteins, biological efficiency of the bound protein, and comparison with standard polystyrene latex particle will be studied. The biological efficiency will be evaluated by testing binding of Factor V antibody and alkaline phosphatase. The addition of fluors and other dyes into the particles for improved visualization under the microscope, other functional groups, scaleup procedures, and extension of these methods to other important proteins would be developed in Phase II.

Title of Project: Microtiter Plate Based Assay System

Principal Investigator: John C. Widman

Awardee Organization: KMS Fusion, Inc.
3621 South State Road
Ann Arbor, Michigan 48106

Telephone Number: (313) 769-8500

This project will develop an instrument capable of automatically performing all liquid processing steps of enzyme-linked immunosorbent assays (ELISA) and related assays. The unit will perform the assays in 96-well Microtiter plates, controlled either by an internal microprocessor or by an external microcomputer. Other features to be incorporated are a Microtiter plate stacker and changing mechanism, a provision for incubation, and a means to minimize evaporation from the wells. The instrument can be used in the pharmaceutical industry for drug testing and process control, in the control of other industrialized biological processes, in testing of meat and agricultural products, and in medical research and clinical laboratories.

Title of Project: Investigations on Diffuse Reflectance

Principal Investigator: N.J. Harrick

Awardee Organization: Harrick Scientific Corporation
88 Broadway, Box 351
Ossining, New York 10562

Telephone Number: (914) 762-0020

Diffuse reflectance (DR) spectrometry is becoming an important technique for characterizing powdered samples; however, surprisingly little is known about the technique, and its use will be limited until the quantitative behavior is more thoroughly understood.

The effect of optical geometry on DR spectra of several types of samples including materials without sharp absorption bands, neat powdered materials (organic materials with weak absorption bands, and inorganic materials with bands of greater absorption), effect of particle size for all samples, and effect of dilution of the samples in KCl will be studied, as will varying the angles of incidence and reflection. The feasibility of measuring the DR spectra of powders dispersed in liquids will also be studied.

Such measurements could have considerable significance in the detection of low levels of drugs and their metabolites in physiological fluids. In addition, because a number of manufacturers produce DR spectrometers that show differences that can (and do) affect the spectra, it is important to determine the optimum geometry for DR spectroscopy so that a consistency among commercial instruments can be obtained.

Title of Project:	Digital Transfer of Histopathologic Images
Principal Investigator:	John W. Sagartz
Awardee Organization:	International Micro Images Route 4, Box 339 Manhattan, Kansas 66502
Telephone Number:	(913) 485-2305

The objective of this project is to develop a cost-effective real-time image processing system for transmission of histopathologic pictures between pathology laboratories.

An image processing system is being developed with off-the-shelf equipment and available software. New software will be developed to make the system operate. A strategy to transmit the pictures over telephone lines, either by sending individual pictures of selected microscopic fields or a composite image of all fields at one time will also be developed. These pictures will be 256 x 256 images per picture and, if the resolution is not sufficient, 512 x 512 images per picture will be investigated.

Phase I will demonstrate whether it is feasible to send a low-cost, high-resolution histopathologic picture. If Phase I of the project is successful, Phase II will develop the market, go into production, and set up prototypye demonstrations in various laboratories for critical evaluation by pathologists.

Development of this system will significantly enhance the dissemination of histopathologic information. This project is an example of the integration of a traditional medical field with the latest technological developments to make a quantum jump in the field of pathological diagnosis.

Title of Project:	Pulse Signals to Cells Using a Unique Perfusion System
Principal Investigator:	John C. Widman
Awardee Organization:	KMS Fusion, Inc. Post Office Box 1567 Ann Arbor, Michigan 48106
Telephone Number:	(313) 769-8500

Cellular response to pulsatile molecular signals, rather than steady-state signals, may be nearly universal and, if demonstrated, will be a discovery of fundamental importance. The aim of this research is to construct and test a unique cell microperfusion system capable of making dynamic measurements online to identify what pulsatile signal characteristics (compounds, pulse height [concentration], pulse width, order, and timing) evoke cellular response.

The perfusion system will be developed and biological experiments will be performed at the Program for the Study of Reproduction and Differentiation of the University of Michigan. This project is expected to establish the feasibility and importance of using dynamic, online, perfusion systems for the stimulation and analysis of cells and tissues in vitro. A family of marketable instruments should evolve, providing powerful, flexible ways to monitor the dynamics of living cells in response to a variety of drug regimens, toxins, environmental samples, or other samples. Such instruments might be indispensable to pharmaceutical houses and industrial firms needing process control of biological processes, and of use in medical diagnosis.

Title of Project:	Adaptation of Cell Markers to Clinical Image Cytometers
Principal Investigator:	Catherine W. Patrick
Awardee Organization:	Laboratory Sciences Institute, Ltd. 1845 Stinson Parkway, Suite 207 Minneapolis, Minnesota 55418
Telephone Number:	(612) 788-9219

This project addresses the commercial potential of performing cell surface marker analysis using monoclonal antibodies tagged with a variety of heavy metal colloids of varying size and color. Currently, cell marker analysis, proven to be clinically important in the detection, diagnosis, and monitoring of human diseases, are performed either manually via fluorescent/light microscopy with its imprecise identification and statistical counting errors or by flow cytometric analysis with a costly capital equipment outlay. The commercial availability of easily visualized, nonfluorescent monoclonal reagents will permit clinical hospital laboratories to perform cell marker studies on existing capital equipment and image analysis systems, which perform routine blood cell differentials in many labs. These image analysis systems are not capable of fluorescence detection which negates their use with existing fluorescent monoclonals.

One aspect of this project will involve the development of such nonfluorescent heavy metal colloid tags that, because of their variable size and color differences, may be used in combination, resulting in savings to the customer. These will be coupled to a variety of commonly used and specialized monoclonal reagents against human leukocytes. This technique will permit direct visualization of the cellular elements spread in a monolayer or thin section manner on standard microscopic slides, and will permit instant cytomorphologic correlation with the cell in question. All new reagents developed will be evaluated by manual and flow cytometric methodologies in a double bind test. Once developed the reagents will be marketed for cell marker analysis using direct visual assessment (manual and/or image analysis systems) as reagents or in kit form for use in the routine clinical laboratory.

A second aspect of this project will attempt to develop and characterize selected murine monoclonal antibodies to human tumor-specific antigens. All resultant monoclonals will be carefully screened and correlated with histopathologic interpretations. The resultant monoclonals will be tagged with the new colloids and with traditional fluorescent dyes for use in manual, flow, and image cytometric systems.

These studies have the potential to improve the level of testing sensitivity for cell marker analysis by manual methodologies through the elimination of problems related to human (eye) detection of fluorescence intensity, as the colloids are assessed by light techniques, and will use existing clinical lab equipment.

Title of Project:	Laser Micropolarimetry
Principal Investigator:	Michael Hercher
Awardee Organization:	OPTRA, Inc. 1727 Revere Beach Parkway Everett, Massachusetts 02149
Telephone Number:	(617) 389-7711

This project is developing an instrument for measuring small amounts of transient birefringence in microscopic biological samples, and will apply it to an existing measurement requirement in the area of neurophysiology. The laser micropolarimeter will be capable of measuring sample birefringence with sensitivity at least 100 times greater than that of currently available techniques, and with spatial and temporal resolutions of 2 microns (diameter) and 1 millisecond, respectively. The basis for the major improvement in instrument sensitivity is the application of a stabilized two-frequency helium neon laser with a heterodyne signal analysis system. This approach directly measures birefringent-induced phase changes in light frequency, circumventing the limitations inherent in the conventional technique, which relies on intensity measurements obtained through crossed polarizers.

In Phase I, a prototype instrument will be used in voltage-clamp experiments to measure the induced membrane birefringence response of the squid axon. Results will be compared with those obtained by conventional methods. Since transient membrane birefringence changes have been associated with neuron action potentials and muscle fiber excitation, there is a community of investigators who will benefit immediately from the project. Birefringence measurements offer an attractive noninvasive alternative to microelectrode methods for membrane potential studies. With a more sensitive and more practical technique for minute polarization measurements, many applications in cell biology and diagnostic pathology are possible.

Title of Project:	Superior Embediment for Light and Electron Microscopy
Principal Investigator:	Jack Radell
Awardee Organization:	Polysciences, Inc. 400 Valley Road Warrington, Pennsylvania 18976
Telephone Number:	(215) 343-6484

This research is intended to provide new soluble plastic embedding resins useful in preparing morphologically superior tissue sections for electron and light microscopy. These polymers, which are not cross-linked, are amenable to a mild solvent treatment that allows penetration by immunoglobulins and other tissue markers of great interest.

Such an embedding resin will minimize the patient cost and the amount of patient biopsy tissue required, and at the same time will increase the diagnostic value from a single embedded block.

The investigators propose the development of polymers that are E-beam stable and capable of being thin-sectioned, thus allowing the physical properties necessary for electron microscopy and light microscopy microtomy. This will be accomplished by incorporating into the polymeric compositions aromatic nuclei that render the polymer electron beam stable. By adjusting copolymer composition, the hardness, solubility, chemical, and staining characteristics of the polymer will be modified to yield the desired sectioning properties. The commercial acceptance of embedding media that meets the criteria proposed is very promising, as researchers and clinical laboratories have need of such media for thin immunodiagnostic test procedures.

Title of Project:	Improved Gel Electrophoresis System for Medical Research
Principal Investigator:	Gerald Entine
Awardee Organization:	Radiation Monitoring Devices, Inc. 44 Hunt Street Watertown, Massachusetts 02172
Telephone Number:	(617) 926-1167

Gel electrophoresis is one of the most widely used analytical techniques in molecular biology and genetics. Typically the separation requires several hours and the gel is then removed and analyzed for the location of the different molecular groups on the surface of the gel.

When used with radioisotopes as labels, the standard practice is to remove the gel and use it to expose film over 24 to 48 hours. This practice is very labor intensive, time consuming, and subject to many forms of error. An alternative approach is to devise a system that would read both the amount of activity and the ultimate location of the molecular groups as the separation is taking place. By obtaining a real-time output as the gel is running, the operator would be able to follow the progress of the separation and obtain timely results.

The investigators propose to determine the feasibility of using such a real-time measuring system for gel electrophoresis of radiolabeled macromolecules. Our preliminary experiments indicate that such a system should be successful and should lead to a significant increase in the data flow from this important analytical technique.

Title of Project:	New Two-Dimensional Solid State X-Ray Detector for Biomedical Research
Principal Investigator:	Michael R. Squillante
Awardee Organization:	Radiation Monitoring Devices, Inc. 44 Hunt Street Watertown, Massachusetts 02172
Telephone Number:	(617) 926-1167

Two-dimensional x-ray detectors are finding increasing use in diffraction studies of biological macromolecules, especially with the advent of high intensity x-ray sources and computer-aided analysis systems. Currently available detectors suffer from performance limitations, maintenance requirements, and/or exorbitant costs. This project is aimed at the development of a large-area single crystal detector with excellent quantum efficiency, no image distortion, and high maximum data rates.

The technology to be used is based on the large-area silicon avalanche photo diode developed for nuclear counting applications and should result in a reliable detector with reasonable costs. Phase I research will be directed at investigating the feasibility of spatially resolved charge collection from both sides of the device and at optimizing the quantum efficiency in the x-ray region. During Phase II these techniques will be used to develop a large-area array detector for eventual production and sale to the molecular biology research community.

Title of Project:	CCD Digitization of Electrophoretic Gels
Principal Investigator:	Brian L. Craine
Awardee Organization:	Western Research Company 5061 West Camino de Girasol Tucson, Arizona 85745
Telephone Number:	(602) 743-7377

This project is applying new two-dimensional, state-of-the-art charge-coupled device (CCD) image detectors to the problem of analysis of proteins by digitization of two-dimensional polyacrylamide electrophoretic gels. Success of this project will result in commercialization of a new product line of medical machinery, more widespread use of electrophoresis in a clinical setting and eventual application of this technology to a family of biomedical imaging problems.

Phase I is providing experimental data for analysis of the parameters required of a CCD digitizer used in this application. It is also providing a quantitative comparison of the advantages of using CCD devices for digitizing as opposed to other, older technologies. These data will serve as a basis for full-scale development of an electrophoretic gel digitizer and related analysis software in Phase II of this project.

Title of Project:	Hydrocarbon Free Extraction Using Supercritical Fluids
Principal Investigator:	Raymond K. Houck
Awardee Organization:	Suprex Corporation 6101 Penn Mall, Suite 300 Pittsburgh, Pennsylvania 15206
Telephone Number:	(412) 661-1707

Technical feasibility research is being performed on the use of supercritical fluids to separate naturally occurring coloring and flavoring pigments from their botanical sources. Supercritical fluid technology is an innovation that substitutes compressed gases, at pressures and temperatures above their thermodynamic critical points, for liquid phase solvents. In this physical state, compressed gases have the solvating power of common liquid solvents, but retain the mass transfer and diffusion properties of a gas. Supercritical fluids are superior solvents for analyzing and purifying a wide range of organic and biological products.

Currently used synthetic food colorants, such as FD&C Red No. 40, are suspected carcinogens. Natural red colorants are a potential alternative; however, current technology for the isolation of these colorants involves extraction with harmful organic solvents such as hexane, methanol, methylene chloride, and acetone. The application of supercritical fluid extraction for this purpose could provide an alternative supply of pure, solvent-free, noncarcinogenic natural coloring and flavoring compounds for food products.

Anthocyanin-containing botanicals will be tested to determine the extractability of their pigment components with supercritical carbon dioxide. The effect of a number of experimental parameters on extraction rate will be studied and extracted pigments will be tested for color value and composition.

Title of Project:	Preparative Chromatography of Proteins
Principal Investigator:	Karen M. Gooding
Awardee Organization:	SynChrom, Inc. Box 110 Linden, Indiana 47955
Telephone Number:	(317) 339-4668

High-performance liquid chromatography has been shown to be an excellent method for the analysis of proteins and peptides such as variant hemoglobins, interferon, and creatine phosphokinase; however, there are no similar supports available for use on a preparative scale. This project proposes to synthesize a series of bonded-phase liquid chromatography supports for the preparative purification of proteins and peptides. Such supports would have high resolution and high capacity, yet also be stable and rigid.

The specific aim of Phase I is to find the optimum support, in terms of resolution and capacity, for preparative chromatography of proteins by bonding a polymeric polyamine coating, a weak anion-exchanger, to many samples of porous silica or other rigid supports. Protein samples such as ovalbumin, serum albumin, and serum would be analyzed on the column to test for capacity and resolution. In Phase II of the research, the synthesis of cation-exchange, hydrophobic, and anion-exchange bonded phases would be optimized on the support chosen in Phase I to provide the highest possible loading capacity for proteins.

The greatest commercial use for such products would be by biotechnological or pharmaceutical companies that are trying to purify proteins and peptides on a large scale.

Title of Project: Correlation of Dynamic Molecular Shape with Activity

Principal Investigator: Richard D. Cramer

Awardee Organization: Tripos Associates, Inc.
6548 Clayton Road
St. Louis, Missouri 63117

Telephone Number: (314) 647-1099

Improvements in correlating biological activity with its most important determinant, molecular shape, should improve the efficiency of drug discovery. A particularly promising method of shape correlation, "DYLOMMS," has been applied at Smith Kline & French to elucidate the gamma-amino butyric acid uptake receptor requirements. Its key features are (1) representation of dynamic molecular shape as a population-weighted composite of, effectively, coarse steric and electrostatic maps of contributing conformers and (2) use of principal components to perform the data reduction implicitly required for such an undetermined problem as shape/activity correlation.

In Phase I the crude current implementation of this method is being converted into an integrated, exportable system, incorporating interactive graphics. In Phase II the approach will be further evaluated.

Title of Project: Differential Viscometer--High Performance Liquid Chromatography/Gel Permeation Chromatography (HPLC/GPC) Detector

Principal Investigator: Max A. Haney

Awardee Organization: Viscotek Corporation
1030 Russell Drive
Porter, Texas 77365

Telephone Number: (713) 359-5966

The long-term objectives of the proposed research are to further develop the differential viscometer (DV) and to demonstrate the potential use of this new instrument for the solution of significant biomedical problems. Specifically, Phase I is intended to accomplish the following: (1) show that the speed and sensitivity of the DV makes it useful in a screening program to detect drugs and other compounds that intercalate with DNA, (2) couple a simple flow injection analysis system to the DV for an alternative approach to the DNA-drug testing, and (3) develop a modified DV for use as an online detector for high-performance liquid chromatography/gel permeation chromatography.

These goals have considerable potential for producing a line of commercial instruments that interface with a wide range of techniques in biochemistry.

Phase II Projects

Title of Project:	Development of the Biological Laser Microprobe Technique
Principal Investigator:	Robert W. Odom
Awardee Organization:	Charles Evans & Associates 1670 South Amphlett Boulevard, Suite 120 San Mateo, California 94402
Telephone Number:	(415) 572-1601 extension 313

Laser microprobe mass analysis (LMMA), employing a high-power pulsed laser and a time-of-flight mass spectrometer, has emerged as a rapid (albeit immature) analytical technique for surface analysis and microanalysis of inorganic and industrial organic solid materials. Unlike charged-particle beam analytical techniques, the use of photon excitation minimizes the concern over specimen electrical conductivity, thereby making the methodology appropriate for biological samples. Combining the inherently sensitive elemental, isotopic, and molecular speciation capabilities of mass spectrometry with a microfocused laser beam (≤ 1 micron) and material consumption that can be limited to only a few molecular layers, LMMA has the potential to contribute major innovative advances to the characterization of biological materials at both the cellular and subcellular levels. What remains to be accomplished to establish the technique as a routine tool for diagnosis and/or biomedical research is the development of reliable methods and procedures vis-a-vis the complex chemical structures normally encountered in biological materials systems. Once these are achieved and implemented, it is anticipated that the technique will assume a role at least equivalent to the electron microprobe in the bioanalytical laboratory.

Title of Project:	Feedback Controlled Oligonucleotide Synthesizer
Principal Investigator:	Mickey S. Urdea
Awardee Organization:	Chiron Corporation 4560 Horton Street Emeryville, California 94608
Telephone Number:	(415) 655-8729

Two fully computer-controlled deoxyribopolynucleotide synthesizers have been produced during Phase I. Over 600 oligonucleotides up to 122 bases have been synthesized. One machine synthesizes one oligomer at a time while the other makes four sequences simultaneously. The feasibility of feedback control of the coupling step without deprotection and of purification of oligomers while bound to a solid support have been investigated.

During Phase II, the feedback system is being thoroughly tested and interfaced to the synthesizer. Appropriate hardware and software will be developed. Also, the DNA purification method will be refined and automated.

DNA synthesis has become an integral part of molecular biology. Even though several commercial oligonucleotide synthesizers have appeared, none is capable of producing oligomers as large and as quickly as can be obtained from the instruments developed in Phase I. Even if other instruments eventually reach this capacity, a feedback system that can correct (not terminate) poor synthesis, coupled with the ability to automatically purify synthetic DNA, should have a reasonable position in the marketplace.

Title of Project:	A Computer System for the Molecular Biology Laboratory
Principal Investigator:	Anne Johnson
Awardee Organization:	DNAStar 1547 Jefferson Street Madison, Wisconsin 53711
Telephone Number:	(607) 251-9284

The advent of rapid, simple methods for sequencing DNA molecules has led to a major new need for the day-to-day use of computers in the typical molecular biology laboratory. The low cost of microcomputers relative to the cost of university or commercial timesharing facilities has generated interest in these small machines as the most cost-effective way to achieve this need.

But molecular biologists wishing to set up a microcomputer must choose hardware from a range of confusing options, and software written by other researchers may be difficult to use and adapt to the hardware chosen. When special hardware such as a digital tablet is involved, the compatibility problem is even more serious. In such a chaotic situation, the biologist must personally spend a great deal of time or hire an expert programmer to get a system up and running.

In the Phase I feasibility study, a DNA software package of over 30 programs was developed and extended. Portions of the software were modified to run on the IBM personal computer. The key problem identified concerns low capacity of the hard and floppy disks of the IBM. In order to hold and manipulate the GENEBANK data base of nucleic acid sequences as well as the analysis software, a capacity of at least 25 megabytes is required and a means to back up and distribute this information more conveniently than by 30 to 70 5-inch floppy disks is needed. The proposed solution is to include a tape cartridge in the system. Phase II is implementing the entire package of software on the chosen hardware to produce a prototype commercial system. When the prototype is ready it will be tested in laboratories. In addition, a number of new programs will be developed for capabilities that so far have not been available for the laboratory microcomputer.

Title of Project:	Development of Menabitan, a Novel Analgesic
Principal Investigator:	Harry G. Pars
Awardee Organization:	HGPARS Pharmaceutical Laboratories, Inc. 763D Concord Avenue Cambridge, Massachusetts 02138
Telephone Number:	(617) 354-2800

No medication with the following characteristics is available for moderate to severe pain: no physical drug dependence liability, low oral toxicity, minimal respiratory center activity, parenteral/oral potency, and long acting. This project's long-term objective is to develop and market such an analgesic from one of its series of cannabinoid analogs, the benzopyranopyridines. Menabitan, a second generation drug showing antinociceptive potency between codeine and morphine, showing no drug dependence liability, and minimal bradycardia in preliminary pharmacologic screens, has been selected. Menabitan acts at a novel, as yet unidentified binding site. Its parent compound, Nabitan, has already proven active orally in humans.

The major goal of this project is to clinically evaluate the efficacy and side effect liability of parenteral Menabitan. To achieve this goal, researchers are (1) preparing a parenteral formulation of Menabitan, (2) performing advanced preclinical pharmacology and toxicology evaluations, and (3) performing early clinical investigations via a dose rangefinding study in volunteers and an efficacy trial in postsurgery patients experiencing moderate to severe orthopedic pain.

Upon successful completion of this effort, private Phase III funding will be obtained to bring parenteral Menabitan to the new drug application stage and to support development of an oral formulation of this drug.

Title of Project:	Digital Control of Rehabilitation/Exercise Machines
Principal Investigator:	James J. Brickley, Jr.
Awardee Organization:	Isotechnologies, Inc. 501 South Greensboro, Building B Carrboro, North Carolina 27510
Telephone Number:	(919) 929-7795

The long-term objectives of this work are twofold: first, to develop adaptive machines that can be used effectively in the evaluation and rehabilitation of muscular deficits due to trauma, disuse, or disease in a broad spectrum of the population, from victims of accidents and chronic musculoskeletal disorders to athletes and the aged; and second, to collaborate with health professionals in collecting and analyzing data, using the unique capabilities of these devices, and to establish a data base to make these data readily accessible. Thus, these machines should be versatile, incorporating active as well as passive exercise capacity, and capable of collecting, archiving, manipulating, and comparing quantitative measurements from treatment protocols.

The specific aim is to develop precise, online feedback regulation of previously designed, instrumented machines, which permit motion in three dimensions and employ electrohydraulic control of resistance. This is to be implemented by using a professional workstation as host computer, communicating through a multiport interface with a programmable controller at each machine. Thus equipped, these machines will have unique capabilities to assist orthopedists, physical therapists, and sports trainers with graded, adaptive protocols based on therapeutic goals and patient characteristics.

Title of Project:	Thermospray HPLC Detectors
Principal Investigator:	Gordon J. Fergusson
Awardee Organization:	Vestec Corporation 2524 Sunset Boulevard Houston, Texas 77005
Telephone Number:	(713) 521-2599

The objectives of this research are to complete the development of new thermospray detectors for high-performance liquid chromatography (HPLC) and to demonstrate the utility of these new detectors for the solution of significant biomedical problems. Techniques for HPLC have evolved rapidly during the past few years, and many important biomedical applications are now well established. A major factor that may limit further rapid development of HPLC is the lack of suitable detectors for many applications. This may be particuarly true for biological samples that are often very complex mixtures containing trace components of interest.

The thermospray transport detector achieves separation of the sample from the solvent by depositing the sample onto a moving continuous belt, which then transports the sample to a gas phase detector. At the detector the sample is vaporized or pyrolyzed so that it can be detected in the gas phase by a gas chromatography detector such as flame ionization, electron capture, or photoionization. The unique feature of the thermospray technique is that the sample is efficiently and completely sprayed onto the belt during the spraying process. In this way the problems associated with earlier transport detectors for liquid chromatography are avoided.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Phase I Projects

Title of Project:	Sensors for In Vivo Monitoring of Blood Gases
Principal Investigator:	Kenneth Abel
Awardee Organization:	The Abel Company Pembroke, Virginia 24136
Telephone Number:	(703) 626-3376

Research is being conducted on optical fiber-coupled fluorescent sensors for the continuous in vivo monitoring of blood gases. The purpose of the project is to identify fluorescent chemical systems specifically sensitive to pH, pO_2, pCO_2, and temperature. From these identified systems, a selection will be made of those compatible for use in a mixed sensor probe. The goal of this study is to minimize the number of separate fibers needed for a low-cost blood gas-sensing radial artery catheter. This study has implications for both improving the quality of intensive care for critically ill patients while reducing costs through reducing the number of clinical laboratory test samples required during the course of treatment.

The commercial market for fully sensed radial artery catheters costing under $65 is estimated at a quarter million units within 5 years of their introduction.

Title of Project:	Developing/Marketing an Asthma Self-Management Program
Principal Investigator:	John A. Winder
Awardee Organization:	Allergy and Asthma Consultants 5300 Harroun Road, Suite 101 Sylvania, Ohio 43560
Telephone Number:	(419) 885-5755

This project has three components. During part I, which will last approximately 3 months, all components required for a self-management program for all asthmatic patients will be developed. This will entail, in part, refining and videotaping portions of a program with proven efficacy, Wheezers Anonymous. In addition, reliability and validity of paper and pencil instruments used to assess the program will be refined and tested.

Part II will feature application of the self-management program to asthmatic adults and parents of asthmatic children. The experimental design involves random assignment of subjects to either an intervention group or a waiting-list control group; this segment of the program will most likely occur in the remaining 3 months of the study. Operating concurrently, Part III will involve a preliminary marketability analysis of the prospect of introducing Wheezers Anonymous to other patients in other settings.

Data gathered during this investigation, regarded as Phase I of a larger investigation on the development and evaluation of a self-management system for asthma, will be analyzed and presented. Information collected and analyzed on marketability of the program will be used to increase use of the materials developed under the auspices of this project.

Title of Project:	Wearable Air Supply for Artificial Heart
Principal Investigator:	Anatole J. Sipin
Awardee Organization:	Anatole J. Sipin Company, Inc. 505 Eighth Avenue, 10th Floor New York, New York 10018
Telephone Number:	(212) 695-5706

The primary objective of the project is the development of a practical wearable air power supply for an implanted pneumatic artificial heart.

This project addresses the concept of a wearable air power supply for a pneumatic heart that has been implanted in an ambulatory patient, and seeks to identify the smallest and lightest pneumatic drive for the application, so that a unit can be continuously worn on a belt or harness without undue discomfort.

A preliminary analysis of a wearable air power supply has been made. Air is supplied by a motor-driven partial-emission centrifugal blower. The air flow is controlled and directed by an electrically piloted pneumatic valve powered by the blower output pressure. A preliminary layout of a package using readily available commercial components has been made. The unit has sufficient battery capacity of 1 hour or more of operation. The total package volume is 56 cubic inches and the weight is 3 pounds, half of which is due to the batteries. Advanced lithium batteries can achieve 5-hour operation or substantial reduction in size and weight.

The wearable air power supply also could be adapted for application as a personal and portable respirator, which could free a patient with respiratory failure from being confined and tethered.

In Phase I a feasibility study for an optimal design of a wearable air power supply for a pneumatic artificial heart is being conducted. The study will identify state-of-the-art and developmental air pump designs, motors, bearings, and batteries. A design configuration will be recommended for development.

Title of Project:	Wearable Respirator
Principal Investigator:	Anatole J. Sipin
Awardee Organization:	Anatole J. Sipin Company, Inc. 505 Eighth Avenue, 10th floor New York, New York 10018
Telephone Number:	(212) 695-5706

Many patients with chronic respiratory failure require mechanical ventilatory assistance to sustain life. Patients treated at home or in the hospital are restricted to a bed-to-chair existence because of the size of existing mechanical ventilatory equipment. A small wearable respirator would free such patients for periods of time from attachment to the bulky equipment, and also increase the number of respirator-bound patients who can be discharged from the hospital setting to a home care situation.

The objective of this project is the development of a practical wearable respirator that is very small and light and that can be continuously and comfortably worn on a belt or similar support.

A preliminary analysis and a preliminary layout of a wearable respirator have been made. Air is supplied by a motor-driven centrifugal blower. The air flow is controlled and directed by an electrically piloted pneumatic valve, powered by the blower output pressure. Based on use of readily available commercial components, the package has a volume of 40 cubic inches and a weight of 2 pounds. The duration of continuous operation is 1 to 4 hours or longer, depending on the demand and the type of battery used.

Such a miniature respirator could be used in an ambulance to provide temporary respiratory support for patients with immediate or developing respiratory failure. The device would also be useful for inter- or intra-hospital transport of patients who require chronic mechanical ventilatory support. Another application would be to provide ventilatory support to potential organ donors being transported to regional organ transplant centers who have suffered irreversible brain death.

In Phase I a feasibility study will be conducted for an optimal design of a wearable respirator. The study will identify state-of-the-art and developmental air pump designs, motors, bearings, batteries, and controls. A design configuration will be recommended for development.

Title of Project:	Swallowable Electrodes for Temporary Cardiac Pacing
Principal Investigator:	Charles E. Yurkonis
Awardee Organization:	Arzco Medical Electronics, Inc. 5757 North Sheridan Road Suite 13A Chicago, Illinois 60660
Telephone Number:	(312) 561-5544

The long-term objective of this project is the development and marketing of easily-swallowed electrodes for temporary transesophageal cardiac pacing. This pill electrode can replace cardiac catheterization in a variety of diagnostic and therapeutic applications, including initiation and/or termination of tachycardias, short-term maintenance of adequate rate in sinus bradycardia, and acceleration of rate to produce stress during echocardiographic or radionuclide studies of ventricular function. With transesophageal instead of catheter pacing, these applications become outpatient procedures with a greatly reduced complexity and cost.

The specific objectives for Phase I are to (1) determine an optimal design for the bipolar transesophageal pacing electrode, (2) implement the design in an electrode that can be enclosed in an ordinary pharmaceutical capsule like the present pill electrode for esophageal electrocardiography, (3) develop new electronic circuits for the special nonpolarizing stimulator to be used in this high-current, switched pacing/recording application, (4) fabricate a flexible, ultrathin silicone rubber sheath to use with the pill electrode to improve fixation and provide for delivery of air and local anesthetic, and (5) design a continuation study in Phase II that will evaluate the electrode/stimulator system under clinical conditions, conceive new clinical applications, and develop a manufacturing and marketing plan for wide use of the technique.

Title of Project: An Automated Hematology Microscope

Principal Investigator: John W. Combs

Awardee Organization: Automated Diagnostic Systems, Inc.
2422 South Walter Reed Drive, Suite C
Arlington, Virginia 22206

Telephone Number: (703) 998-0088

Phase I of this project is exploring via computer simulation, in a very high-speed computer, the use of state-of-the-art RCA charge-coupled devices (CCD) in an automated diagnostic microscope (ADM) for imaging and analyzing blood cells stained with a quantitative fluorescent technique that allows accurate characterization of all the types of cells encountered in peripheral blood. Digital images prepared from calibrated microphotographs of white blood cells, platelets, and red cells will be used to represent the output of the CCD imagers in the computer simulation. The simulation will then be used to design the prototype instrument. Phase I will also include the structuring of the simulated image data into parameters related to the quantity and morphology of cell constituents (DNA, nuclear size and shape, heterochromatin, cytoplasmic volume and shape, hemoglobin, specific granules, lysosomes, and RNA). Software will be developed and explored for using these parameters to classify and describe blood cells. The parameters will then be used to guide the development of cell analysis software. The technique of computer simulation should very significantly aid in speedy production of a functioning prototype ADM in Phase II.

The ADM represents a significant advance in blood cell imaging because of its high resolution and sensitivity that capitalize on a quantitatively interpretable specimen. The ADM will expand the data base describing normal and abnormal (including neoplastic) blood and bone marrow cells, providing quantitative diagnostic parameters that are not currently available. The first-level design goal is, however, to provide all of the currently available hematologic tests made on blood cells in a completely automated mode.

The ADM will be extremely cost-effective. It will perform all the tests done on blood cells in the clinical hematology laboratory at least as fast and in more detail than current instrumentation. The ADM will be capable of the diagnostic discrimination of blood cells, and will be easily adapted to the utilization of monoclonal antibodies in cell identification and characterization. These factors should stimulate commercial interest.

Title of Project:	A Networked Computer-Mediated Smoking Cessation Program
Principal Investigator:	Jay T. Tooley
Awardee Organization:	Behavioral Health Systems 650 Victory Boulevard, Suite 3E Staten Island, New York 10301
Telephone Number:	(212) 447-3127

The purpose of the project is to determine the cost-effectiveness, the acceptability, and commercial applications of an interactive computer-mediated smoking cessation program delivered online through an established international computer network. The intent is to make readily available to the growing numbers of individuals and groups who have access to personal computers at home, schools, hospitals, and work an inexpensive, effective smoking cessation program. Phase I results are expected to prove the cost-effective and client-acceptability information necessary to pursue the research and development into Phase II. Positive results in Phase I would dictate broader trials in Phase II in a variety of settings such as hospitals, schools, group practices, and corporations.

Successful results in Phases I and II would have important implications for the feasibility of providing both commercial and noncommercial clinical and human services through computer networks on an international scale.

Title of Project:	Magnetometer for Measurement of Lung Particulates
Principal Investigator:	Duane B. Crum
Awardee Organization:	Biomagnetic Technologies, Inc. 4174 Sorrento Valley Boulevard San Diego, California 92121
Telephone Number:	(619) 453-6300

The pulmonary toxicity of environmental and occupational noxious particulates is often increased by impairment of normal clearance mechanisms prolonging the particulates' time in the lung. Clearance mechanisms vary widely among individuals, resulting in a highly variable sensitivity to such contaminants. Up to this time, detailed studies of clearance mechanisms and particulate accumulation in human subjects have not been possible because of the excessive radiation associated with existing techniques. The recently developed technique of magnetopneumography (MPG) now offers a noninvasive, purely passive means to conduct such studies. It also offers the potential for routine screening of individuals to measure clearance times and hence to classify people according to their susceptibility to lung damage in various environmental conditions. MPG can also be used to monitor dust accumulation for people in environments known to be hazardous over time; when critical levels of particulate accumulations have been reached, those individuals may be removed from the environment. An example would be the monitoring of coal dust accumulation in coal miners.

The first generation of superconducting magnetometers constructed by the investigators and used in the pioneering MGP work have certain serious limitations that make widespread clinical research impractical. This project will identify the sources of those limitations and minimize or eliminate them. This will be done in consultation with the medical research group that conducted most of the pioneering research. The primary Phase I effort will study the instrument drift sources (flux motion in super-conducting materials, magnetic relaxation effects, and others) resulting from exposure to the direct current (DC) fields required by the technique. Various new pickup coil arrays will be evaluated to obtain improved sensitivity deep in the lungs and to reduce measurement time. Upon resolution of these two issues, a preliminary design of a complete instrument suitable for extensive clinical studies will be prepared.

In Phase II, that prototype instrument will be produced and made available for clinical studies. Successful completion of these studies will lead to commercialization and production of an MPG instrument package.

Title of Project:	Potassium-Ion Fiberoptic Medical Sensor
Principal Investigator:	Edmond Green
Awardee Organization:	Biomedics, Inc. Post Office Box 971 Mercer Island, Washington 98040
Telephone Number:	(206) 392-8391

The objective of this project is to demonstrate the feasibility of a membrane-sensor system suitable for use in a miniature fiberoptic potassium-ion sensor (optrode) for continuous monitoring in body fluids.

Potassium levels are commonly monitored during cardiac surgery, diabetic acidosis, renal failures, and other acute conditions. Potassium levels can be very labile, and thus monitoring requires frequent measurements, with substantial labor and lab charges. A relatively inexpensive, disposable, and continuous probe would give immediate clinical information and would be cost effective.

The specific aims of the Phase I project are to: (1) synthesize a dye molecule that is sensitive to the concentration of potassium-ion in the pathophysiological range; (2) develop a means of immobilizing the K+ sensor dye molecule within a semipermeable membrane; (3) construct a working model of the fiberoptic probe; and (4) determine the effectiveness of the probe by <u>in vitro</u> analysis of body fluid with known K+ concentrations.

The longer-term Phase II objectives are to miniaturize the K+ probe and combine it into a multiparameter probe for monitoring several components, such as O_2, CO_2, and pH.

Title of Project:	Anatomical Substitutes with Proclivity for Cell Lining
Principal Investigator:	Peter H. Duquette
Awardee Organization:	Bio-Metric Systems, Inc. 9932 West 74th Street Eden Prairie, Minnesota 55344
Telephone Number:	(612) 941-0080

The implants field or "spare-parts medicine" is a young (approximately 25 years) health care activity requiring intensive input from engineers, materials scientists, and physicians. An all-purpose medical synthetic has not been found. Biomaterials are needed for many functions and environments within the body, requiring a wide variety of physical properties for their construction and stable functioning. A major difficulty is acquiring a biocompatible surface in combination with the required physical properties (for example, strength, elasticity, permeability, and flexibility) that will be stable over a long period of use in the body.

A major advance in biomaterials technology would result from tailoring the surface of preformed physically optimized implant devices to provide the proclivity for rapid overgrowth of a stable natural cell surface lining. Cell attachment factor proteins involved in the control of endothelial cell migration, attachment to substratum, and growth have been purified and chemically and biologically characterized. Photochemical cross-linking reagents and reaction technology for effective coupling of active proteins to the surface of a wide variety of biomaterials have been developed and demonstrated in this laboratory. A plan is proposed for combining the expertise and materials from a leading cell attachment factor laboratory with those of a surface chemistry-biocompatibility laboratory, to provide a facile surface modification of substitute blood vessel materials for the promotion of rapid endothelial cell surface overgrowth.

The current world market for implantable devices and artificial organs is estimated to be between $3 and $4 billion. The demand grows in direct proportion to advances in materials development technology. This proposed technology is expected to provide biocompatibility for additional industrial materials already available.

Title of Project:	Isolation of Endotoxin-Inactivator (EI) from Human Plasma
Principal Investigator:	Yu-Lee Hao
Awardee Organization:	Biotech Research Laboratories, Inc. 1600 East Gude Drive Rockville, Maryland 20850
Telephone Number:	(301) 251-0800

It has been known for 30 years that human plasma has the ability to diminish the pyrogenicity of endotoxins derived from Gram-negative bacteria. Numerous studies have since been reported in the literature demonstrating that plasma contains an endotoxin-inactivator that reacts with the lipid moiety of lipopolysaccharides of endotoxins, thus rendering those toxins nonpyrogenic. In the plasma fractionation industry, manufacturers often find that their final clinical plasma products, such as albumin, immune globulins, and antihemophilic factor are pyrogenic, thus resulting in the loss of the entire lot because it is no longer suitable for intravenous injection. The monetary loss each year due to pyrogenic products are in the hundreds of thousands, if not millions, of dollars.

A large-scale method to depyrogenate clinical albumin has been developed. It consists of mixing plasma with pyrogenic albumin followed by a precipitation step to remove all plasma proteins including the inactivator and endotoxins, leaving only albumin in the supernatant. This method has been included in the amendment of the albumin license of the New York Blood Center. However, it is obvious that this method cannot be used for depyrogenation of other clinical plasma products because of different purification steps involved. This research project is developing a large-scale method of isolating this inactivator by affinity adsorption from large plasma pools before plasma fractionation by ethanol so that it can be added to any pyrogenic plasma products without adversely affecting their purity or safety. The inactivator-depleted plasma could still be used for routine plasma fractionation. Attempts will also be made to make insoluble the inactivator on a matrix (for example, Sepharose) so that any pyrogenic parenterals intended for injection can be made nonpyrogenic by mixing with EI-Sepharose followed by filtration.

Title of Project:	Feasibility of an In-Vivo Plasmapheresis Device
Principal Investigator:	Allen R. Grahn
Awardee Organization:	Bonneville Scientific 918 East 900 South Salt Lake City, Utah 84105
Telephone Number:	(801) 359-0402

This project is investigating the feasibility of a system that will use ultrasonic radiation forces to selectively move and separate the cellular constituents of blood. It will be possible to develop a device that can perform plasmapheresis within the hypodermic needle. In this device there will be no restriction of fluid flow, but the formed elements of the blood will be acted upon differentially by the generated forces, which will expel or repel them from the needle. If this goal can be achieved, it will allow the withdrawal of plasma directly from the donor or patient, leaving the cellular components unaffected in the blood stream. This device, a solid-state electronic instrument, will be technically much simpler than current centrifugal or filtration devices. It total extracorporeal blood volume will be less, it will not require anticoagulants or other drugs to be given to the patient, and it will not subject the cells and platelets to the trauma of centrifugation or filtration.

The proposed device will find several applications. Because operating and disposable costs will be low, it can replace the manual procedure used in the collection of source plasma for production of plasma-derived products, and it will replace the centrifugal or filtration devices used to provide large amounts of plasma for therapeutic plasma exchanges or for removal of specific plasma agents that are being used as successful therapies for many chronic diseases that have heretofore defied conventional therapy.

Title of Project:	Angulation Mechanism for Catheters and Angioscopes
Principal Investigator:	William C. McCoy
Awardee Organization:	Catheter Research, Inc. 11339 Valley Meadow Drive Zionsville, Indiana 46077
Telephone Number:	(317) 873-3155

Medical science has progressed to the point that catheters and angioscopes can be used for direct visualization of the interior surfaces of the heart and coronary arteries. The primary hindrance to further progress in this field is the lack of a miniaturized angulation system. This research concept suggests that proprietary materials be incorporated into the tip of a catheter or angioscope to make them maneuverable.

When Phase I and II are completed, this research will provide a catheter/angioscope with the following features:

1. The deflection will take place in the tip.
2. The angulation system will be microminiature and will result in a minimal increase in catheter diameter.
3. The body of the angioscope will not have added stiffness.
4. The system can be used with fiber optics or other microinstrumentation.

Phase I funds will be used to provide safe entry into the canine model. Phase II will advance the research from canines into humans.

When the research is completed, the medical community will have the ability to manipulate a variety of devices in an X, Y plane. This technology is applicable to radiologic and cardiac catheters, angioscopes, and fiber optics used by lasers.

Title of Project:	Closed-Loop Pharmacological Control of Heart Rate
Principal Investigator:	Sherman M. Seltzer
Awardee Organization:	Control Dynamics Company 555 Sparkman Drive, Suite 1414 Huntsville, Alabama 35805
Telephone Number:	(205) 837-8510

Using the drug esmolol, a fast-acting, water-soluble beta-1 adrenergic blocking agent, it is possible to control tachycardia in patients during general anesthesia and after operations. The goal of the Phase I research is to generate a closed-loop system to control tachycardia using esmolol. The design would be accomplished using available digital design tools. The ultimate aim is to mesh the heart rate control system that would result from this effort with established methods for pharmacologic control of blood pressure in patients under general anesthesia and in the postoperative period. The synergistic result would be a multi-input, multi-output control system where two combined controllers would work in concert to achieve the desired control.

Phase I research requires the use of dogs infused with bolus doses of esmolol to produce the time-response data required to obtain a plant description. A mathematical model will be defined and a simulation composed. Using established system analysis and compensator design techniques, the desired controller may be easily designed and tested with the simulation. Microcomputer code would be generated during Phase II, involving testing of the control algorithm on animal and human subjects. Interest in Phase III has been manifested by the developers of the drug as well as manufacturers of monitoring, computer, and infusion pump equipment.

Title of Project:	Purification of a Bacterial Protease Inhibitor
Principal Investigator:	John C. Cheronis
Awardee Organization:	Cortech, Inc. 3115 East 40th Street Denver, Colorado 80216
Telephone Number:	(303) 333-0038

This project is developing a protease inhibitor that can be safely administered to patients who have ongoing elastin destruction as a major feature of their disease. Such diseases include those in which phagocyte action (inflammation) has occurred on connective tissue targets--pulmonary emphysema, pneumonias, adult respiratory distress syndrome, dermatologic inflammatory processes and infections, vasculitis, and autoimmune disorders.

The investigators have already demonstrated a unique inhibitor of human neutrophil elastase in several bacterial species. Preliminary purification and characterization of one of these inhibitors have been performed. The investigators must now document that this inhibitor is capable of preventing some of the diseases mentioned in laboratory animal studies and, at the same time, document that this inhibitor can be safely administered. After the efficacy and safety of this product has been documented in animal studies, application will be made to begin human studies.

In Phase I, the substantial portion of the animal studies using rabbit and rat experimental models of disease is being completed. Primarily, the ability of this inhibitor to prevent experimentally induced emphysema and to mitigate against the permeability changes in animal models of the adult respiratory distress syndrome is being studied. During Phase II, further animal studies will be added and human studies will begin. If all the potential of this product is realized, then this medication may become the mainstay of therapy for many chronic and acute diseases for which there is no effective therapy and that affect tens of millions of individuals in this country and around the world.

Title of Project:	Antimicrobial Impregnation of Silicone Rubber
Principal Investigator:	John B. Newkirk
Awardee Organization:	Denver Biomaterials, Inc. 6851 Highway 73 Evergreen, Colorado 80439
Telephone Number:	(303) 674-5294

The long-term objective of this project is to test and make commercially available an already defined laboratory process for impregnating antimicrobial agents into silicone rubber, using the Denver Hydrocephalus Shunt as a prototype device. Successful results from this study will be applied later to many commercial devices that bring silicone rubber into chronic contact with living body tissue. This innovation is expected to produce major humanitarian benefits because of the lowered incidence of infection.

The specific aims of this project are to: (1) confirm prior studies in which silicone rubber, impregnated with one of several antibiotic drugs, was shown to have significant antimicrobial influence on selected bacterial strains; and (2) apply the impregnation process to the Denver Shunt and test its antimicrobial efficacy in vitro and in vivo.

Phase II will consist, in part, of extending the types of tests done in Phase I and of applying the results of Phases I and II to the development of processes and facilities for commercial production of antibiotic-treated silicone rubber products.

In Phase III the Denver shunt will be made commercially available as soon as possible, with the protection of infused antibiotics a standard feature. Thereafter, other commercial implant products will be similarly treated.

Title of Project:	Evaluation of a Retrovenous Myocardial Perfusion System
Principal Investigator:	Jeffrey L. Peters
Awardee Organization:	Deseret Research Company 520 Wakara Way Salt Lake City, Utah 84108
Telephone Number:	(801) 584-3222

Retrovenous diastolic myocardial perfusion (RVDP) with oxygenated blood via the coronary sinus and coronary veins has been shown experimentally to provide 45 percent of the normal coronary blood flow. RVDP therapy could significantly alter the morbidity of patients with coronary artery disease and acute myocardial ischemia. Current experimental RVDP catheters require a second arterial source of oxygenated blood and abnormally elevate venous pressures.

Single, triple lumen RVDP catheters are being fabricated and bench tested with a roller pump, pulse chamber, membrane oxygenator, and control module. Safe boundary conditions of RVDP pressure and flow will then be evaluated by acute experiments in three normal sheep for feasibility and tc determine if mean coronary sinus and venous pressures can be reduced with active coronary venous decompression. RVDP will then be applied in three normal sheep for 6 hours to test for any myocardial or vein damage. RVDP will also be applied in three sheep half an hour after coronary artery ligation to determine percent salvage of injured myocardium "at risk." RVDP will have a significant therapeutic and commercial impact on the treatment of myocardial ischemia and cardiogenic shock, as a drug delivery system (for example, Streptokinase, cardioplegia) and as a routine therapy for patients undergoing percutaneous transluminal angioplasty, cardiac diagnostic procedures, or intra-aortic balloon pumping.

Title of Project: Time-Variant Data Compression and Retrieval

Principal Investigator: Vladimir A. Shvartsman

Awardee Organization: Electronic Design & Research, Inc.
770 Medical Towers South
Louisville, Kentucky 40202

Telephone Number: (502) 589-9968

As prevention becomes more important in the field of modern medicine, efficient data collection and recording become a must. The objective of this project is to devise a system with a new type of data processing algorithm that allows a drastic reduction in memory needed for data storage.

It will be achieved by using an innovative time-variant data compression technique. The main difference between traditional methods in data storage and this project is that the project technique will store the length of time an input signal is in the same aperture and the direction of the slope but not the value of the signal itself. The data storage rate automatically adapts to the slope of an input signal, thereby maintaining the accuracy of the stored signal. This will save considerable memory space by eliminating nonessential data.

During Phase I knowledge is being gained, an inexpensive portable data storage device is being built, and the device is being tested on medical data collection. In Phase II this technique will be used in a portable arrythmia detection device, the efficiency of data compression will be tested, and a compression technique for reducing data and equal succeeding samples will be developed.

Title of Project: Implantable Miniature pH Electrode

Principal Investigator: Larry Swette

Awardee Organization: Giner, Inc.
14 Spring Street
Waltham, Massachusetts 02154

Telephone Number: (617) 899-7270

A novel miniature catheter-mounted electrode capable of reliable and real-time pH measurements in blood and tissue is being developed in this project.

The principle of the pH-sensing electrode is based on the reversible hydrogen electrode, which is the ultimate standard for pH determination. Difficulties associated with glass pH electrodes for in vivo measurements can, therefore, be alleviated.

This pH-sensing electrode, when used with an indwelling pCO_2- and pO_2-sensing electrode, will provide real-time physiological information necessary for ventilation management and acid-base balance maintenance in intensive care, operating rooms, and research laboratories.

Title of Project:	Tissue Equivalent Immobilizer for Digital Angiography
Principal Investigator:	Roger J. Malcolm
Awardee Organization:	HealthCare Affiliates, Inc. 23961 Calle de la Magdalena Suite 203 Laguna Hills, California 92653
Telephone Number:	(714) 855-8728

The overall objective of this project is to develop a tissue-equivalent immobilization device (TEID) for various radiologic procedures. The initial impact of this project will be in the area of digital subtraction angiographic (DSA) runoff studies allowing, for the first time, precise image reregistration for time-mode subtraction of images acquired before and after injection of contrast media into a patient's vascular system. Advantages of using TEID include: increased patient comfort, use of the full dynamic range of the imaging chain, increased digitization accuracy, assured immobilization, and ease of equipment handling. The stated objective will be achieved through systematic development of engineering design specifications, prototype construction, and evaluation using an existing prototype DSA system with computer-controlled table-top movements for runoff studies.

Phase II will entail modification of the initial design according to specifications derived from Phase I, development of an ideal attenuating medium, adaptation of TEID for therapeutic radiologic procedures, production, and advanced placement of TEID in service.

Title of Project:	Blood Cell Washing Using Shear Centrifugation
Principal Investigator:	Donald W. Schoendorfer
Awardee Organization:	HemaScience Laboratories, Inc. 2807 Catherine Way Santa Ana, California 92705
Telephone Number:	(714) 261-7900

Demand for washed red blood cells is increasing. This is in part due to awareness of transfusion-related diseases such as hepatitis and Acquired Immune Deficiency Syndrome (AIDS). Existing technology for red cell washing is inefficient because a significant amount of final washed product is often lost in the process. This project is to investigate the extension to cell washing of a new core technology of blood separation being developed. The basis of this technology is a revolutionary new technique that exposes a membrane filter to a fluid containing elements to be filtered. External inertial forces are used to prevent formed elements in the blood from adhering to the membrane. This technology will allow reduction of the surface area of the membrane filter from 10 to 100 times that used in current blood filtration systems based on flat plate and hollow fiber technologies and therefore permit a significant cost reduction. The technology is continuous instead of batch operated so it is inherently faster in its processing time than existing devices, and no washed product is lost. Important commercial applications of this new technology include deglycerolization of frozen blood, autotransfusion, and fresh wash of blood before transfusion.

By using specific fluid mechanical and hematological analysis, the investigators propose first to investigate the phenomena involved in this new core technology relevant to cell washing. By empirical analysis on prototype models, four specific strategies will be investigated. These strategies are related to the modification of the forces exposed to the blood over the filter, to the introduction and mixing of wash solution, and to the removal of spent wash solution and all blood elements other than red cells. This feasibility study will conclude with a foundation for an optimized design dedicated to red blood cell washing. The foundation will be built upon in-depth Phase II development.

Title of Project:	Monoclonal Antibodies to Apolipoprotein A-1
Principal Investigator:	Paul J. Price
Awardee Organization:	Hybridoma Sciences, Inc. 4690 Hammermill Road Atlanta, Georgia 30084
Telephone Number:	(404) 493-1902

Lipoproteins are high molecular weight, water-soluble complexes composed of lipid and one or more specific proteins. They are grouped according to their density as determined by ultracentrifugation. Plasma low-density lipoproteins (LDL) contain approximately 75 percent lipid and 25 percent protein and function as a major carrier of cholesterol. Apolipoprotein B is the structural protein moiety of LDL. An elevated level of apolipoprotein B has been reported to be a marker of coronary artery disease. In addition, reduced levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein A-1 have also been reported to be markers. HDL contains approximately 50 percent apolipoprotein with 32 percent of the lipid component being cholesterol and 65 percent of the apolipoprotein being A-1.

Monoclonal antibodies with specificity for apolipoprotein B from human plasma LDL have previously been developed. Because of the role that lipoproteins play in the pathogenesis of atherosclerosis, their quantitation is important not only for metabolic studies but also for the characterization of dyslipoproteinemias. The specific aims of this project are to develop and characterize monoclonal antibodies to human apolipoprotein A-1 (Phase I) and to use these antibodies as reference standards for the isolation or identification of apolipoprotein A-1 and as sensitive indicators of coronary artery disease (Phase II).

Title of Project: A Personal Computer-Based Outpatient Biofeedback Trainer

Principal Investigator: Charles H. Sathrum

Awardee Organization: INET Corporation
536 Weddell Drive, Suite 1
Sunnyvale, California 94089

Telephone Number: (408) 734-0311

Numerous disorders, including hypertension, cardiac arrhythmias, and vascular headaches are treatable through biofeedback training reinforced by patient practice. In many cases, biofeedback training may be preferred to the use of drugs for treating specific disorders.

The objective of this project is to develop an inexpensive, easily used biofeedback trainer for clinical use and particularly for home practice. Features of the personal computer, including memory, graphics capabilities, and educational and specialized software, would be used to develop a product superior to the current generation of outpatient biofeedback trainers. During Phase I, the investigators will evaluate: features required for acceptance by clinicians; input modalities to satisfy treatment requirements; currently available biofeedback systems and input pickups; best suited candidate personal computers and their available data acquisition systems; and feedback modalities shown best to facilitate learning.

A result of Phase I will be the development of a functional specification from which the prototype system can be constructed, tested, and validated in Phase II; this will also include a preliminary conceptual design, covering operations, display graphics, and cost data. Phase I work will determine the most productive applications of these techniques and the availability and requirements of hardware and software components.

Title of Project:	Percutaneous System for Energy Transmission
Principal Investigator:	Adrian Kantrowitz
Awardee Organization:	LVAD Technology, Inc. 70 Gallogly Road Pontiac, Michigan 48055
Telephone Number:	(313) 338-4167

A percutaneous access device (PAD) is an artificial aperture in the skin intended to establish a permanent passageway between the inside and the outside of the body without interfering with host homeostasis. PAD's have many potential uses and have been studied extensively in relation to permanently implanted prostheses that augment the action of the failing heart. Current cardiac assist systems depend on electrical or pneumatic power, which must be transmitted across or through the skin. As yet, however, a PAD that is reliable in long-term use has not been developed.

To prevent infection, the major cause of PAD failure, the investigators postulate that PAD design must provide for (1) control of epidermal proliferation and migration in proximity to the implant, and (2) attenuation of local strain. A PAD hypothesized to meet these requirements is being studied in rats and swine. Its neck (the transcutaneous portion) is nanoporous; a Dacron velour-covered flange joined to the neck is placed subdermally. Before implantation, autologous fibroblasts are cultured onto the PAD neck, forming a multilayer coating. The results indicate that PAD's prepared in this way inhibit epithelial downgrowth, whereas uncoated implants fail as a result of epidermal migration and infection.

The objective of this Phase I project is to transfer and extend to sheep (which increasingly are used for full-scale testing of cardiac assist systems) the methods evolved in swine. Specific aims are to: (1) adapt techniques for in vitro fibroblast proliferation and collagen production on the PAD neck to sheep cells; (2) adapt surgical techniques for PAD implantation to sheep; and (3) develop a protocol for long-term evaluation in sheep of a functioning PAD transferring power to an implanted heart assist device.

The long-range goal is to qualify a PAD and make it commercially available for clinical use in conjunction with a system for treatment of patients in severe, chronic left heart failure. In addition, availability of the PAD for sheep will facilitate its adoption for preclinical evaluation of various mechanical heart assist systems by others. This program will also lead to improved PAD's for other commercial applications such as vascular access for kidney dialysis and skeletal attachment of prosthetic limbs.

Title of Project: Ventilator Alarm Using Inductive Plethysmography

Principal Investigator: Karl H. Maret

Awardee Organization: Maret Consulting Services
3541 Mount Alvarez Avenue
San Diego, California 92111

Telephone Number: (619) 292-7038

An improved ventilator monitor and alarm system is being developed that uses the Respitrace Inductive Plethysmography principle to quantitate actual tidal volume and minute ventilation in patients who are chronically ventilator dependent. Alveolar hypoventilation or overinflation of the patient can be detected if ventilation deviates from preset limits. Respiration is monitored by a real-time microprocessor-based instrument and alarm system that is calibrated for each patient and ventilator. The initial prototype will be completed and patient evaluation begun during Phase I.

Potential advantages of this system include: (1) better warning of ventilator malfunction or disconnection, due to true monitoring of patient respiration; (2) potential for long-term data logging of ventilation changes that may reflect a circadian rhythm and/or vary with changes of lung mechanics or disease; (3) assessment of feasibility of weaning patients off ventilators; and (4) increased reliability of proper ventilator performance in home care environments with potential cost savings in home nursing care personnel. Future validation of this technique might lead to the development of improved home apnea alarms for neonates and patients with central or obstructive sleep apneas, or apnea monitors for postoperative or intensive-care unit patients in hospitals.

Title of Project:	Development of Pediatric Catheters That Reduce X-Ray Use
Principal Investigator:	William McCormick
Awardee Organization:	McCormick Laboratories, Inc. 481 Great Road Acton, Massachusetts 01720
Telephone Number:	(617) 264-4500

The objective of this project is to commercialize a totally new endotracheal tube with a special sensing instrument to determine the tube's position. The tube and sensing instrument concept is designed for use in pediatric respiratory support procedures. The new device offers three distinct health care benefits over existing technologies: (1) reduction in x-ray exposure in pediatric patients, which is particularly significant in those patients who require long-term intubation, (2) improvement of operating room pediatric anesthesiology procedures by providing noninvasive, real-time, direct determination of endotracheal tube position in the trachea, and (3) reduction in x-ray-related costs of patients requiring long-term respiratory support procedures.

The new tube incorporates in its wall an electromagnetic field interference element that is detected by the sensing instrument. The technical feasibility and the potential clinical use of engineering prototypes have already been suggested by a preliminary study in cadavers that compared the tube position as determined by the instrument with conventional x-ray methodology.

This project will develop production prototypes of new pediatric endotracheal tubes that will be suitable for clinical evaluation. Following completion of this research, a clinical evaluation of the developed product will be initiated for pediatric patients.

Title of Project:	Improved Blood Sampling and Analysis
Principal Investigator:	James S. Davidson
Awardee Organization:	Moleculon Research Corporation 139 Main Street Cambridge, Massachusetts 02142
Telephone Number:	(617) 547-2353

This Phase I project is directed toward aspects of clinical blood analysis in which there has been little progress in recent years: sample collection, preparation, and colorimetry. The investigator will seek to incorporate automatic membrane filtration directly into disposable blood samplers to obtain cell-free extracts without centrifugation, and will investigate the feasibility of additional labor savings based on colorimetric plasma analyses conducted directly within transparent membranes. Both the filtration and the thin film colorimetry will rely on the unique properties of Poroplastic film, a transparent permselective membrane in which many normal liquid-phase reactions can readily be conducted. Since plasma obtained using membranes lacks the high molecular weight proteins found in centrifuged plasma, it should be particularly suitable for enzymatic analysis of important low molecular weight solutes. The thin film colorimetry to be investigated will not rely on semiquantitative reflectance measurements, such as those used in home glucose indicators, but on enzymatic schemes in combination with transmission spectrometers.

The underlying goal of the entire project will be to provide acceptable clinical blood analyses with a much reduced investment of clinical labor. Eliminating sample-handling steps such as those associated with centrifugation will also remove a major source of dangerous laboratory error--misidentification of samples during pouring operations. Another associated benefit, reduction in analytic turnaround times, could itself be lifesaving in cases such as severe electrolyte imbalance or diabetic coma.

Title of Project:	Miniature Drive for Jarvik-7 Blood Pump
Principal Investigator:	Milton S. Isaacson
Awardee Organization:	NuTech Industries, Inc. 5885 Wolf Creek Pike Trotwood, Ohio 45426
Telephone Number:	(513) 837-2685

The objective of this project is to develop a 12-volt direct-current VDC external drive system for the Jarvik-7 blood pump that is small and lightweight enough to be worn in a side-mounted vest so that it is completely portable. The proposed system will replace the current pneumatic system, which weighs approximately 375 pounds. The new fully developed system, which will be hydraulic and powered by batteries, will occupy approximately 775 cubic inches (in two pieces) and weigh less than 5 pounds. The much discussed "quality of life" of the artificial heart recipient will be greatly improved by such a device.

The Phase I effort will prove (in vitro) the feasibility of driving the implanted Jarvik-7 with an external hydraulic pump, and will make the first reduction in size of the electronic controller and will demonstrate the external drive system's capabilities through in vivo animal testing. The Office of Technology Assessment estimates that 84,000 persons a year are candidates for artificial hearts. The program has the potential for improving the artificial heart's system weight, portability, and reliability to make the device more acceptable to thousands of potential users.

Title of Project: Fiber Optic Continuous Flow Measurement Catheter

Principal Investigator: Charles M. Davis

Awardee Organization: Optical Technologies, Inc.
8200 Greensboro Drive, Suite 550
McLean, Virginia 22102

Telephone Number: (703) 821-3952

From independent research, investigators have determined that a need exists in the medical community for an instrument that is capable of accurately and continuously monitoring blood flow in vivo. A unique fiberoptic sensor has been designed that can be used for such measurements in large and small arteries. This technique overcomes many of the disadvantages of current methods and provides the following major features: (1) continuous measurement of blood flow, (2) accuracy (± 1 percent), (3) small size (can be made as small as .3 millimeters diameter), (4) reliability and safety (non-thrombogenic), and (5) direct measurement and display of flow pulse shape (flow versus time).

The specific aim of this project in Phase I is to build a prototype of the flow catheter and to validate its predicted performance under laboratory conditions. The commercial applications for this disposable catheter are very promising. With more than 1 million cardiovascular procedures and more than 300,000 bypass surgeries performed annually, the continuous and accurate measurement features of the catheter will find use in diagnostic procedures, critical care monitoring, angioplastic procedures, and continuous cardiac output monitoring. Satisfactory demonstration during Phase I will set the stage for commercialization of the product during Phase II.

Title of Project:	Robotic Device for Regulated Cardiovascular Exercise
Principal Investigator:	Cord B. Sengstake
Awardee Organization:	Psytech, Inc. 3151 Northwest Vaughn Portland, Oregon 97210
Telephone Number:	(503) 223-0205

A generally accepted premise is that cardiovascular health, with its associated increase in longevity, is best maintained by regular aerobic exercise. A common aerobic strategy is to establish a target heart rate and then attempt to exercise at an intensity that maintains the heart rate at that target value.

The long-term objective of this project is to develop a microcomputer-controlled exercise cycle. This technologically innovative robotic device will automatically adjust the workload to maintain the user's heart rate at the target level. The user will sit in a semirecumbent position and grasp electrodes connected to a cardiotachometer circuit. As the user pedals, the heart rate will be compared to the target rate and the workload will be automatically adjusted.

The specific aims during Phase I are to: (1) develop an engineering prototype, complete with associated software, and (2) develop the research protocols necessary to test the prototype's efficacy as a safe and efficient commercial aerobic device suitable for the elderly and for those who may have impaired cardiovascular function. During Phase II of the project, the engineering prototype will be tested in accordance with the research protocols and then modified as needed for the development of the prototype.

Title of Project:	Ventricular Function Monitor for Active Patients
Principal Investigator:	Gerald Entine
Awardee Organization:	Radiation Monitoring Devices, Inc. 44 Hunt Street Watertown, Massachusetts 02172
Telephone Number:	(617) 926-1167

To increase the basic understanding of the cardiac function and to improve techniques to aid in the diagnosis of heart disease, the investigators are conducting research on an improved method of evaluating myocardial function in active patients. This approach involves the use of a very compact, vestlike instrument that uses nuclear medicine techniques to measure the ejection fraction of the high ventricle on a beat-by-beat basis. The system is designed to be worn by ambulatory patients over an 8- to 16-hour period and uses an on-board cassette recorder to store the nuclear and the corresponding electrocardiograph data.

The basic concept appears quite promising. However, the present nuclear sensor is too large and is too insensitive to be suitable for clinical work. The investigators propose to develop a new sensor that will be sufficiently sensitive, reliable, and compact to make this concept a reality. In Phase I, they will demonstrate the possibility of making such sensors. In Phase II they will complete the sensor and associated microelectronics for a working clinical prototype.

Title of Project:	Spectroscopic In Situ Analysis of Sweat
Principal Investigator:	William T. Joines
Awardee Organization:	SCI Development Corporation 800 Eastowne Drive, Suite 209 Chapel Hill, North Carolina 27514
Telephone Number:	(919) 493-6003

The long-term objective of this project is to offer to hospitals and large group practices a fast, accurate, safe, painless, and inexpensive device for diagnosing cystic fibrosis in patients of any age.

The technique is spectroscopic in situ analysis of sweat. Phase I of the research plan is intended to produce a clinical prototype of the device. This research plan is an outgrowth of earlier research that produced the governing theory and laboratory equipment. Phase I objectives include the optimization of the technique and equipment and the resolution of remaining questions. The specific aims of Phase I research are the development of an optimized power supply, a photomultiplier detector, a computer control system, a glass electrode, and a portable cart, and the chemical analysis of sweat induced by the system.

After Phase I research is completed and a clinical prototype is produced, a clinical testing period will follow. The results of this testing will provide the basis for Phase II work. Phase II research and development will result in a commercial version of the in situ spectroscopic device, which will then be offered to hospitals and group practices for the routine screening and diagnosis of cystic fibrosis.

Title of Project: Holter Analysis Using Artificial Learning

Principal Investigator: Donald E. Gustafson

Awardee Organization: Scientific Systems, Inc.
54 Rindge Avenue Extension
Cambridge, Massachusetts 02140

Telephone Number: (617) 661-6364

The purpose of this research project is to complete the development of the automated Holter ECG analysis system, which is based on artificial learning methods using statistical models. The present system has been tested on a standard annotated data base and found to give superior performance to current systems for which published data are available. Following completion of the Holter analysis software, a vigorous in-house and independent evaluation of system performance will be conducted to demonstrate clinical efficacy. This approach is expected to significantly reduce human intervention and the cost of automated Holter analysis. The ultimate aim is to develop a nearly error-free real-time monitor that automatically will record all electrocardiographic events of clinical importance and transmit either routinely or as required a complete report to the physician or user. The potential cost benefits would allow a more rapid penetration into the clinical, epidemiological, and research areas of cardiac dysrhythmias, particularly as they relate to sudden cardiac death.

Title of Project:	**Development of a Noninvasive Cardiopulmonary Monitor**
Principal Investigator:	**Ingvar E. Sodal**
Awardee Organization:	**Sodal & Bowman Company** **216 Sentinel Lane** **Boulder, Colorado 80302**
Telephone Number:	**(303) 444-1444**

The objective of this project is to develop a practical monitoring system that noninvasively and continuously measures every significant parameter associated with oxygen and carbon dioxide transport. The system would have the additional features of requiring minimal patient contact and being noninterfering to gas exchange or any monitored parameters. Thus, the system would be available for monitoring patients ranging in disease severity from critically ill to normal. Monitoring would be applicable to newborn to adult patients, and for activities ranging from sleep to exercise.

The uniqueness of the methodology lies in (1) the use of the lung as a noninvasive port from which all significant gas exchange information is available by analysis of tracer gas components, and (2) the simultaneous measurement and analysis of a sufficiently large and independent set of tracer components to provide characterization of all essential elements of the complex gas exchange process.

The technologies required to support the methodology are (1) high-powered computer technology with efficient software, and (2) mass spectroscopy, which has a combination of sensitivity, frequency response, dynamic range, and accuracy not yet found in practical instruments. The necessary computer power is now available at a practical cost. Also, because of recent advances in mass spectrometer technology, the development of a mass spectrometer with the technical specifications, operational practicality, and sufficiently low cost to support the development of a practical monitor appears feasible.

Firmly establishing such feasibility is the goal of Phase I of this project. The commercial development of the total monitor is the goal for Phase II if Phase I is successful.

Title of Project:	An Extrapulmonary Blood Gas Exchange Device
Principal Investigator:	J.D. Mortensen
Awardee Organization:	Technical Research Associates, Inc. 420 Chipeta Way Research Park Salt Lake City, Utah 84108
Telephone Number:	(801) 582-8080

A multichannel tubular device containing ultrathin walled tubes, permeable to oxygen and carbon dioxide, is being designed and fabricated for use as an extrapulmonary blood gas-exchange device. The product is intended to be inserted into the subject's vena caval system, entering into the right common femoral vein and exiting from the right external jugular vein. Oxygen is passed through the lumina of the hollow tubes while the subject's venous blood flows around the external surfaces of the hollow tubes. Oxygen and carbon dioxide pass across the gas-permeable membrane constituting the walls of the intravenous tubes, increasing the oxygen content and decreasing the carbon dioxide content of the blood within the subject's vena caval system.

In Phase I of this research and development effort, the design and materials for the device will be developed and/or selected, a prototype device will be fabricated, techniques will be developed for its insertion and operation, and its efficacy in transferring oxygen to carbon dioxide from circulating blood will be assessed. These performance evaluations will be conducted in vivo using large dogs as the experimental animals. Biocompatibility of the device will be screened by assessing the pathologic effects, thrombotic and/or embolic sequellae, and hematologic changes in the animals.

If feasibility is demonstrated by this Phase I study, Phase II will further develop and optimize the safety and efficacy of the device by in-depth development and evaluation studies in preparation for Phase III commercialization, production, and clinical utilization of the device. It should have wide clinical applicability to hospitalized patients needing improved oxygenation and carbon dioxide removal.

Title of Project: ^{13}C-Labeled Sterols as Diagnostics: New Synthesis

Principal Investigator: Sun-Shine Yuan

Awardee Organization: Tracer Technologies, Inc.
225 Needham Street
Newton, Massachusetts 02164

Telephone Number: (617) 964-4800

The project relates to the synthesis of ^{13}C-multilabeled cholesterol and sitosterol as potential diagnostic agents. Hypercholesterolemia has been implicated as a primary risk factor in coronary heart disease, yet major questions regarding cholesterol absorption, transport, reverse transport, and disposition remain to be answered because of the lack of a safe, convenient, nonradioactive tracer methodology. Thus, stable isotope-labeled dietary sterols in clinical protocols, combined with mass fragmentography, can be expected to aid the elaboration of indices for such parameters as sterol pool size, transit time, volume distribution, and clearance.

The synthetic approach requires disconnection at C-22 of the sterol side chain and resynthesis with the labels positioned in the isopropyl terminus at C-25, -26, and -27, the latter being derived from $^{13}C_3$-acetone. One of the project tasks is the development of pathways conservative toward the isotope; optimization of yields in the 10-20 percent range are expected. Additionally, the program calls for development of an A-ring degradation and resynthesis via the Robinson annelation to give $^{13}C_4$-labeled sterols. A repertory of various incrementally labeled A and/or chain-labeled sterols can then be envisioned for application in simultaneous studies by multiple routes of tracer administration.

Phase II Projects

Title of Project:	An Implantable Anastomosis Patency Monitor
Principal Investigator:	David Giuliani
Awardee Organization:	Biomedics, Inc. 1145 12th Avenue, Northwest Issaquah, Washington 98027
Telephone Number:	(206) 392-8391

Failure of an anastomosis is one of the most significant problems in microsurgery. All existing techniques to monitor transplanted tissue suffer from one or more problems. No technique is suitable for continuously monitoring tissue that is buried below the surface. The goal of this research project is a product that overcomes the disadvantages of existing methods and is low enough in cost for widespread acceptance.

The investigators' instrumentation approach uses a miniature ultrasonic transducer mounted at the end of small catheter. The transducer is placed next to an anastomized vessel and held in place with dissolvable sutures. The probe can be withdrawn after several days of monitoring. The instrument will measure blood flow continuously; its theory of operation is based on Doppler ultrasonics and the ensonification of a vessel with a Gaussian surface, and takes advantage of the proximity of the vessel to the probe.

The investigators will build on the Phase I feasibility study to refine the instrument for relative blood flow measurements and to test the unit clinically by comparing results with existing methods (clinical appearance, laser Doppler, and PO_2) and with clinical case histories. They will also pursue instrumentation approaches that allow an absolute measurement of flow.

Title of Project:	Improved Methods of Red Blood Cell Measurement
Principal Investigator:	James W. Bacus
Awardee Organization:	Cell Analysis Systems, Inc. 600 South Hoyne Chicago, Illinois 60612
Telephone Number:	(312) 226-5193

The objective of this research is to bring new techniques of red blood cell analysis, for enhanced anemia diagnosis and hematological blood smear evaluation, to general usefulness in the clinical hematology laboratory. First, the investigators are adapting the technology involved to the bench microscope environment by developing a small, compact, solid-state intelligent logic module, custom-designed for this analysis and task and attachable to standard microscopes. This system will be a prototype for commercial application. Second, the investigators will more clearly define the diagnostic potential of the hemoglobin concentration distribution, a major area of technological innovation in this research. This will be studied by simultaneous measurement and comparison of RNA content using the fluorescent stain thioflavin T, hemoglobin concentration using Soret absorption techniques, and transferrin binding using fluorescent monoclonal antibody probes, all in the same individual cells. Third, the investigators will further develop the diagnostic profile of the quantitative red cell morphology (QRCM) test. This will involve the collection of case data for further expansion of prototypic blood conditions, study of nonspecific anemias associated with other primary diseases, and blood conditions under treatment. These techniques provide a new investigative tool for clinical medicine, resulting in enhanced, more efficient, anemia diagnosis.

Title of Project:	Diastolic Pressure Determination by Phase Discrimination
Principal Investigator:	Kuo-wei Chang
Awardee Organization:	Industrial & Biomedical Sensors Corporation 1345 Main Street Waltham, Massachusetts 02154
Telephone Number:	(617) 891-4201

Although diastolic blood pressure is a uniquely defined parameter, its determination is uncertain when a conventional sphygmomanometer is used. A technique based on phase discrimination is described that allows determination of the diastolic pressure without the dilemma of choosing between Phase IV, Phase V, and other criteria. When a Riva-Rocci cuff is inflated, a time lag generally exists between the arrival of the arterial upstroke and the generation of Korotkoff vibration. This time lag decreases steadily as the cuff pressure is lowered, and diminishes as the cuff pressure approaches the true diastolic pressure. The diminution of this time lag is easily detected electronically and can be a more objective, reliable, and accurate criterion for diastolic pressure indexing.

The feasibility of the phase discrimination technique has been established in the Phase I effort. As expected, a diastolic pressure can be uniquely determined through simple time measurements. Diastolic data yielded by phase discrimination were found to agree statistically with those obtained by manual auscultation. With justification from Phase I findings, this Phase iI study is intended to correlate the diastolic pressure based on phase discrimination with those obtained through direct arterial measurements through indwelling catheters.

Title of Project:	**Screening Test for Cystic Fibrosis Carriers**
Principal Investigator:	**Edward G. Bernstine**
Awardee Organization:	**Integrated Genetics, Inc.** **31 New York Avenue** **Framingham, Massachusetts 01701**
Telephone Number:	**(617) 875-1336**

Cystic fibrosis (CF) is the most common lethal genetic disease affecting the white population in the United States and Europe. Although adequate diagnostic tests are available to identify affected homozygous individuals, there is no method available for detecting heterozygous carriers of the disease allele. The goal of this project is to use recombinant DNA technology to gain the information necessary to design a test for CF gene carriers. In Phase I, permanent lymphoblastoid cell lines were established from blood samples of more than 121 members of an extended CF pedigree. This family contains 22 separate sibships with 36 affected individuals. All sibships can be traced back some nine generations to a common ancestor. The lymphoblastoid cell lines have been established to provide a permanent source of DNA from family members.

In Phase II, this DNA will be used to determine genotypes of family members at loci defined by restriction fragment length polymorphisms. Data from each marker locus will then be analyzed for genetic linkage of the marker to the CF gene. The discovery of a marker linked to CF would immediately yield information concerning the chromosomal localization test for inheritance of CF in the children of known carriers. It is also the necessary first step before chromosome-specific cloning techniques can be applied to cloning and characterizing the defective gene. Information concerning the nature of the primary defect will then be used to design a reliable test for CF gene carriers that could be used to screen all adults in the general population.

Title of Project:	**Parent-Delivered Education for Childhood Asthma**
Principal Investigator:	Elanna S. Yalow
Awardee Organization:	IOX Assessment Associates 11411 West Jefferson Boulevard Culver City, California 90230
Telephone Number:	(213) 391-6295

In recognition of the substantial human distress and societal cost associated with childhood asthma, this project's objective is to develop sets of demonstrably effective educational materials to be used in the management of childhood asthma. Three sets of parent-delivered educational materials, each targeted for a different age group, will be developed according to an empirically based revision strategy in which the educational materials can be revised until they consistently promote their intended outcomes. Those outcomes, identified during Phase I of the project by a national panel of experts in the treatment and education of children with asthma, focus on significant behavioral, knowledge, and affective goals that must be accomplished in order for a successful asthma-management program to be initiated. Each of the outcomes will be measured by a criterion-referenced assessment device that will serve not only as the focus of instructional development, but also will gather evidence of the instructional materials' effectiveness. Central to all three sets of instructional materials will be the child's use of a peak-flow monitoring device as a key to proactive asthma management. Finally, rather than rely exclusively on self-management, the new educational materials will stress cooperative management of childhood asthma by children and their parents, physicians, and teachers.

Title of Project:	Continuous Monitoring of Doppler Cardiac Output
Principal Investigator:	Stephen R. Barnes
Awardee Organization:	Lawrence Medical Systems 2849 152nd Avenue, Northeast Redmond, Washington 98052
Telephone Number:	(206) 881-1300

The purpose of this research is to optimize a system for continuously monitoring cardiac output and systemic vascular resistance by the use of Doppler ultrasound from the esophagus, to evaluate the accuracy of the technique, and to demonstrate its clinical utility in patient management.

This will be accomplished by: (1) quantifying the anatomical relationship between the esophagus and the ultrasonically accessible portions of the ascending and transverse aorta in humans using commercially available pulsed-Doppler ultrasound imaging equipment; (2) developing a measurement system optimized for human anatomy; (3) evaluating the accuracy in humans by comparison with alternative techniques; (4) determining the effect of large variations of afterload, preload, and contractility on the relationship between the esophageal measurement and conventional methods using a dog model; and (5) evaluating the system efficacy in patient management through the development and testing of patient management protocols based on the use of continuous hemodynamic monitoring.

This work will provide a substitute for higher risk methods of cardiac diagnosing and will provide the physician a means to continuously monitor hemodynamics while titrating drugs or inducing anesthesia, and will greatly enhance the physician's ability to manage the anesthetized patient.

Title of Project: CO_2 Angiography Injector Development

Principal Investigator: Robert J. Hirko

Awardee Organization: Pathfinder Enterprises
2510 Southwest 14th Drive
Gainesville, Florida 32608

Telephone Number: (904) 392-0961

Angiography with standard contrast media is often painful and occasionally causes hypersensitivity reactions in patients. Digital subtraction x-ray techniques have made possible the use of the gas carbon dioxide as a contrast agent for arterial and venous imaging. No carbon dioxide injectors produced for this project are currently being marketed. The investigators characterized carbon dioxide flow in catheters used during angiography and have identified operational ranges for a gas injector to be used during angiography.

During Phase II of this project the investigators will design and construct several prototype injectors for carbon dioxide angiography. These units will be able to handle both standard dye as well as gas, and will possess microprocessor-based monitoring and control. The units will be evaluated in actual clinical operation at three different hospitals. The design that proves superior in performance, ease of operation, and safety will then be produced.

Title of Project: Development of an Ultrasonic Blood Cell Separator

Principal Investigator: Sam L. Sparks

Awardee Organization: Technical Research Associates, Inc.
410 Chipeta Way, Suite 222
Salt Lake City, Utah 84108

Telephone Number: (801) 581-8080

The objective of this research project is to guide the development of an efficient and novel instrument to remove plasma from flowing whole blood. Beginning with the Tube-Cell technology developed in Phase I, a step-by-step research and development effort is planned to demonstrate a unique method to separate plasma by ultrasonic banding of cellular components. Several versions of the instrument will be constructed in a scheduled design-test-redesign protocol containing 11 achievement milestones. The final version of the Helicol Plasma Separator will be disposable and suited for later clinical studies. In the last quarter of the second year, one or more of these disposable separators, together with full technical and experimental documentation, will be readied for transfer to a Phase III agent company.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

Phase I Projects

Title of Project:	Development of an Automated Digital Nerve Latency Meter
Principal Investigator:	Ronald P. Bak
Awardee Organization:	Bak Electronics, Inc. 687-L Lofstrand Lane Rockville, Maryland 20850
Telephone Number:	(301) 869-3700

The objective of this project is to develop a device for taking automated digital nerve latency measurements and displaying the results on an LED display readout. The device is intended for medical testing of motor nerve conduction velocity and nerve latencies. This diagnostic and prognostic test is used for a large number of medical and surgical disorders. Testing is to be acccomplished using state-of-the-art electronic design techniques to develop an instrument that will measure accurate and reproducible nerve latencies by noninvasive stimulation and recording techniques. The device will be easily portable, operable by medical personnel without specialized training, and priced in the thousand dollar range.

Title of Project:	Implantable Stimulating Microelectrodes
Principal Investigator:	David K. Wong
Awardee Organization:	Giner, Inc. 14 Spring Street Waltham, Massachusetts 02154
Telephone Number:	(617) 899-7270

As the use of neural stimulating electrodes has increased, more attention has been directed toward studying their possible adverse side effects. This is especially true for applications that require chronic stimulation at high-current densities. The risk of tissue damage, which is generally believed to be associated with the toxic species formed electromechanically at the electrode tissue interface, has been hindering the progress in neural stimulation. The objective of this proposed program is to develop high surface area "double layer"-type stimulating electrodes suitable for the electrical stimulation of neural elements for treatment of various neurological disorders. Specifically, the investigators plan to prepare and characterize high surface area carbon and gold microelectrodes. In addition, the investigators propose to demonstrate their operating modes experimentally. After successful long-term in vitro testing, these microstimulating electrodes will be fabricated and delivered to the sponsoring agency in the form of completely finished microstimulating electrode assemblies for in vivo testing in Phase II.

Title of Project:	Portable rCBF System for Real Time Diagnostics
Principal Investigator:	Gerald Entine
Awardee Organization:	Cerebral Monitoring Systems 44 Hunt Street Watertown, Massachusetts 02172
Telephone Number:	(617) 926-1167

Regional cerebral blood flow (rCBF) is an important parameter of brain function in acutely and chronically ill patients. Instruments currently available for measurement of rCBF are large and immobile, and lack the flexibility and utility required to study rCBF in multiple situations such as the operating room and outpatient services.

The investigators propose to split the process of rCBF measurement into a portable microprocessor-based data acquisition device and a high-speed host computer capable of fast data analysis, long-term data storage, and graphical report generation. By employing a new detector technology, solid-state cadmium telluride (CdTe) detectors, which will be more stable and lighter weight than detectors currently available, will be developed.

This project is a joint effort between a manufacturer of CdTe detectors and an instrumentation research and development establishment to develop a mobile rCBF measurement system with high-speed graphic output and multiuse capability. In addition, experts in the fields of data analysis and clinical rCBF from the Bowman Gray School of Medicine will be consulted for their experience and expertise.

In the Phase I project, the investigators will demonstrate the feasibility of developing such a portable device using new low-voltage solid-state cadmium telluride detectors. The system functions will be split into a portable data collection device and a nonportable data analysis, storage, and reporting system, and communication between the two units will be achieved by telephone. The reliability of telephone communications and development of appropriate algorithms for error detection and correction will be investigated. Development of lightweight, stable CdTe detectors, which have been used reliably in other commercial and military devices, will add a higher degree of reliability and mobility to the system. Studies will be undertaken to determine an optimal design for their use in rCBF measurements. Based on experience and preliminary feasibility studies, the investigators expect no problems in demonstrating a working data collection system.

Title of Project:	Electropolymerized Insulating Films for Electrode Implants
Principal Investigator:	Victor R. Koch
Awardee Organization:	Covalent Associates, Inc. Post Office Box 3129 Saxonville Station Framingham, Massachusetts 01701
Telephone Number:	(617) 877-8053

The successful artificial stimulation of living tissue by electrode implantation holds forth the prospect of a visual prosthesis for the blind and a cochlear prosthesis for the deaf, as well as use of hitherto paralyzed limbs. A key problem in developing an electrode implant technology base is maintaining point sources of bare metal at the tip of an insulated wire that reproducibly delivers known amounts of electrical stimulation over long periods of time. The percutaneous saline environment and flexing of the implant seriously degrade the adhesion of the insulating coating to the wire, thereby increasing the electrode area with concomitant failure of the device.

During Phase I of this program, the investigators propose to generate electrochemically thin, coherent polyphenylene oxide coatings onto platinum wire substrates from phenolic monomers. Previous work has shown these coatings to manifest excellent adhesion to metallic substrates due to chemical bond formation between the substrate and polymer as it is formed in situ. The integrity of these coatings will be assessed by SEM and ESCA. Electrochemical techniques designed to assess the coatings' resistance to saline will also be applied.

Phase II work will focus on indepth chemical, electrochemical, and mechanical evaluation of the optimized coatings. Biocompatibility experiments will also be carried out so that by the end of Phase II hardware may be supplied to the sponsoring agency for in vivo studies.

Title of Project:	Computerized Written Communication for the Deaf
Principal Investigator:	Sandra E. Hutchins
Awardee Organization:	Emerson & Stern Associates 13674 Boquita Drive Del Mar, California 92014
Telephone Number:	(619) 481-3242

The deaf in the United States are isolated from both hearing persons and each other. A primary cause of this isolation is the absence of a commonly accepted written form of American Sign Language (ASL). A recently devised symbol set called Sign Writing has been well received, yet its dissemination has been limited by the need to produce the symbols by hand.

This effort will computerize word processing software for Sign Writing and then investigate the psycholinguistic and ergonomic issues involved in the design of a keyboard or similar device tailored to the needs of signers. The primary objective is to determine the feasibility of an input device whose operation uses motor sequences that run congruent to, rather than counter to, the motor activities inherent in Sign production.

Potential commercial applications include Sign typewriters for consumer use; Sign typesetting software and systems; software packages and tools for linguistic research; software data bases for other forms of movement recognition; alternate data entry systems for the physically handicapped; portable ASL-to-English translators; Sign teletypes; and Sign animation for educational use. No such software or devices now exist.

Title of Project:	Signal Processing Hearing Aid
Principal Investigator:	Marshall Long
Awardee Organization:	Marshall Long/Acoustics, Inc. 1629 Stanford Street Santa Monica, California 90404
Telephone Number:	(213) 829-4311

The long-term goal is the development of an all-in-the-ear signal-processing hearing aid. The design of the hearing aid would incorporate the following novel features:

1. Feedback and level control will be achieved by a probe microphone placed within the proximal end of the hearing aid earmold to accurately determine the actual sound pressure level at the eardrum.

2. The input signal will be amplified in individual one-third octave frequency bands. Amplification will be limited to a subject's loudness discomfort level as determined by separate testing for each individual.

3. Amplification will be selectively based on the behavior of the input signal. Amplification activation can be based on a combination of absolute level, change in level, average change in level over a given time, number of zero crossings over a given time, or other time domain functions. The most appropriate amplification activation function will be determined through testing.

The goal of the first 6 months of the project will be to breadboard a working model of the processor using available off-the-shelf components. This will result in a cigar box-sized processor that can be connected to an existing ear mold transducer for testing. The initial performance will be measured using a Kemar mannequin. Initial process control will be by means of a microcomputer.

Title of Project: Design Moving Platform for Vestibular Assessment

Principal Investigator: Lewis M. Nashner

Awardee Organization: Neurometrix
1120 Northwest 20th Avenue, 2nd Floor
Portland, Oregon 97209

Telephone Number: (503) 229-8442

The goal of this project is to develop for commercial purposes and market a movable platform system for the diagnostic screening and treatment evaluation of patients with vestibular equilibrium disorders and vertigo. During Phase I a concept for testing that evolved over 11 years of research will be realized by designing a movable platform structure and hydraulic power system appropriate for clinical uses. The movable platform system will be lightweight, compact, easy to operate and service, safe, and as cost-effective as possible. Future plans call for fabrication and placement of prototype systems in selected clinical environments. Performance of the prototype equipment and methods for presentation of results to the clinician will be evaluated before full-scale commercial production.

Title of Project: Computer Automation of Platform Vestibular Assessment

Principal Investigator: Lewis M. Nashner

Awardee Organization: Neurometrix
1120 Northwest 20th Avenue, 2nd Floor
Portland, Oregon 97209

Telephone Number: (503) 229-8442

The goal of this project is to develop for commercial purposes and market a movable platform system for the diagnostic screening and treatment evaluation of patients with vestibular equilibrium disorders and vertigo. During Phase I, a computer-automated system will be developed so that test protocols that evolved over 11 years of research can be carried out by a clinical technician and then readily interpreted by the physician. The system will be menu driven with adequate operator overrides for safety and pacing of tests. The system will also score the test results and give the physician a concise summary. The long-term goals call for placing a number of prototypes in selected clinical settings and evaluating their effectiveness. The development of a centralized data base accessible by all platform users, based upon the standardized protocols, is also planned.

Title of Project:	**Excitatory Amino Acid Antagonists as Antiepileptic Drugs**
Principal Investigator:	David C. U'Prichard
Awardee Organization:	Nova Pharmaceutical Corporation Wade Avenue, Post Office Box 21204 Baltimore, Maryland 21228
Telephone Number:	(301) 788-0522

This is a Phase I project where funding is sought to set up a drug discovery and development program, leading to new and improved drugs to treat epilepsy by the investigators. Although there are 16 major types of antiepileptic medications in use in the United States, none has proven completely effective, and many of the most commonly prescribed compounds give rise to significant and prevalent adverse side effects. It is generally recognized at the sponsoring agency and elsewhere that there is a clincial need for new, more selective, and effective, antiepileptic agents.

A volume of recent basic research indicates that epilepsy may be a neurodegenerative process precipitated by excessive stimulation of hippocampal or temporal lobe neurons, with subsequent cell death. Excitatory amino acids acting at specific receptor sites have been implicated in this process, including endogenous brain excitotoxins, such as quinolinic acid. Drugs acting as specific antagonists at one or more of the distinct subtypes of excitatory amino acid receptors may hold promise as useful and efficacious antiepileptic agents. One such compound, (-)-2-amino-7-phosphonoheptaoic acid (-APH) has already been shown in animal tests to possess significant anticonvulsant activity. The investigators propose to institute a program to develop and screen APH analogues to achieve increased potency and oral efficacy, leading ultimately to clinical trials of a lead compound. Overall, the program will consist of chemical synthesis, screening at the receptor level in binding and biochemical experiments (to be correlated with activity in simple in vivo anticonvulsant screens), followed by more detailed receptor autoradiographic analysis, single unit electrophysiology, and EEG studies, with promising lead compounds. Subsequently, routine toxicologic and bioavailability determinations will be undertaken. Phase I will establish the correlative receptor, biochemical, and behavioral screens for excitatory amino acid antagonist activity in -APH and a series of analogues to be synthesized.

Title of Project:	Speech Recognition and Communication Disorders
Principal Investigator:	Brian L. Scott
Awardee Organization:	Scott Instruments Corporation 1111 Willow Springs Drive Denton, Texas 76205
Telephone Number:	(817) 387-9514

Speech recognition technology will eventually aid speech therapists in the many time-consuming drill and practice sessions necessary for effective therapy. The question being asked in this project is whether the technology is sophisticated enough to be of benefit. Resources assembled to answer this question include the cooperation of the Division of Communication Disorders at North Texas State University; an Apple-based authoring system designed for implementing courseware using voice input and output (the system has already been tested as a tool for foreign language training); and the expertise of a company dedicated to speech recognition technology and applications.

The approach is divided into four steps. The first is to identify, observe, and record specific therapists and clients engaged in targeted repetitive therapies. The second is to author brief, specific lessons for use in therapy. The third is to train the therapists to use the system. The fourth is to record the client's progress and the therapist's time involved. The subjective question to be answered is how well the client and therapist accept the system. The objective questions are whether the therapist can provide the client with comparable or superior service in less time, and which, if any, repetitive tasks can reasonably be accomplished with current technologies.

Title of Project:	Study of Silicone Insulating Systems
Principal Investigator:	Thomas D. Talcott
Awardee Organization:	Talcott Development, Inc. 2630 Walnut Avenue, Suite F Tustin, California 92680
Telephone Number:	(714) 731-9105

Silicone elastomers, coatings, and sealants, along with other materials, have received extensive evaluation and development for use as electrical insulation for neural prostheses and devices. All materials still, however, exhibit unsuitable long-term adhesion characteristics when exposed to the corrosive effects of body fluids and electrical stress. Additional failures of silicones in inflatable mammary prostheses and even aquarium sealants point to certain types of oils and chemical bonds that should be avoided in the materials. Some primers contribute to adhesion retension when exposed to boiling water; others are detrimental.

Although two programs, on insulating materials and adhesion, are underway, these programs are hampered by the proprietary nature of silicones and other insulating materials. The proposed approach differs in that extremely pure silicone polymers crosslinkers and other ingredients will be formulated into insulating materials. Silicone systems, starting with monomers, polymerization procedures, other chemicals, and catalysts will be studied in an attempt to demonstrate suitable adhesion and stability by better control of the presence of oils, macrocyclics, crosslinkers, and ionizable atoms. Cyclic voltametry will be used to evaluate the retention of adhesion of various silicone materials (elastomers and primers) bonded to the noble metals and other materials used in electrodes, leads, and electronic packages.

Polymerization methods and polymer purification procedures will be selected to reduce the level of oils and contaminates. The completeness of cure and presence of oils will be monitored by Gel Permeation Chromotography (Waters).

Successful demonstration of the causes of adhesion failure will allow for the demonstration of commercially usable insulators in Phase II.

Phase II Projects

Title of Project:	Skin Vibrators and Wearable Aids for the Deaf
Principal Investigator:	David Franklin
Awardee Organization:	Audiological Engineering Corporation 9 Preston Road Somerville, Massachusetts 02143
Telephone Number:	(617) 628-1435

The long-term objective of this project is to make single- and multiple-channel wearable tactile aids available on a commercial basis. The specific aims during this study are following:

1. To develop and evaluate small efficient vibrotactile transducers of the type described in the Phase I study. This type, which is of the magnetic solenoid design, would appear to satisfy the requirements for most single- and multiple-channel wearable aids in the near future. During Phase III these transducers would be made commercially available.

2. To develop hybrid versions of the processing electronics used in the experimental wearable aid, the Tactaid I, which would be adaptable for use in both single- and multiple-channel aids of various designs. The purpose of the hybridization is to reduce packaging size. These hybrids would be evaluated and made available commercially during Phase III.

3. To combine items 1 and 2 into a miniature single-channel wearable aid and subject it to extensive evaluation in a controlled clinical setting. This item would also be made available commercially during Phase III.

The investigators are confident that a single-channel aid of this type would help to aid the language development of the nearly 150,000 school-age profoundly deaf children in this country. While such an aid may also be of significant help to profoundly deaf adults, such data have not yet appeared in the literature.

Title of Project:	Improved Sensitivity Neuromagnetometer
Principal Investigator:	Duanne B. Crum
Awardee Organization:	Biomagnetic Technologies, Inc. 4174 Sorrento Valley Boulevard San Diego, California 92121
Telephone Number:	(619) 453-6300

The precise localization of electrical activity in the brain is of clinical importance in cases of partial epilepsy for which surgery is considered, as well as for other neurological disorders. Current methods are invasive and occasionally inaccurate. Biomagnetometers offer a totally noninvasive means of localizing brain activity, particularly evoked response and the interictal epileptic spike. However, the single-channel systems require long averaging times and frequent repositioning. This requires measurement times too long for clinical studies of large numbers of patients.

In Phase I, the investigators developed techniques reducing overall single-channel system noise well below 20 feet per hertz and allowing much shorter averaging times. In Phase II, the investigators will use these results to develop a complete 19-channel neuromagnetomer system that is suitable for clinical research and that will perform measurements up to 200 times faster than previous systems. New techniques will include electronic noise cancellation and indirect refrigeration, allowing for eventual replacement of liquid helium by cryocoolers. This system will offer the unprecedented ability to simultaneously measure activity at many points around the skull at frequent intervals, resulting in a much improved spatial and temporal resolution and the capability to deal with large numbers of subjects.

Title of Project:	Improved Vestibular Caloric Test System
Principal Investigator:	Douglas S. Antler
Awardee Organization:	ICS Medical Corporation 1785 Cortland Court Addison, Illinois 60101
Telephone Number:	(312) 495-2150

The primary objective of this project is to develop instrumentation and associated test methodology that will offer researchers and clinicians markedly improved information from the caloric test of the vestibular system. Subordinate objectives are to allow the test to be administered more easily, with less patient discomfort, and in a more cost-effective manner.

In Phase I, an experimental setup of the instrument was constructed and bench tested to verify its ability to deliver the temperature patterns desired.

Phase II will consist of the development and testing of the instrument's control system, the refinement of the design into a production model, and the testing of various protocol on human subjects to verify improved intrapatient test stability and to determine new stimulus patterns. Instrument design will take place at the researching company and patient testing will be done at Johns Hopkins University.

Title of Project:	Auto Screener for Epileptoform EEG Data
Principal Investigator:	James S. Bryan
Awardee Organization:	Telefactor Corporation Union Hill Building West Conshohocken, Pennsylvania 19428
Telephone Number:	(215) 825-4555

The second phase of this two-phase program will develop a microprocessor unit to screen 16-channel EEG data in real-time and mark those epochs that contain epileptoform activity. The unit would be marketed as a modular addition to data collection systems already sold for long-term epilepsy monitoring. Realization of such a unit involves adapting principles already proven and running on computers such as the PDP 11/60. Modern microprocessor techniques can now permit recognition modules to cost in the $15,000 range. The most widely accepted of the university-developed programs is that developed at Montreal Neurological Institute by J. Gotman.

In Phase I of this project, it was demonstrated that Gotman's programs can be recoded to run on a microprocessor faster than the required rate. The Phase II study has three objectives: (1) augmentation of the existing program for improved seizure detection accuracy, (2) integration with existing EEG monitoring and review equipment, and (3) clinical evaluation.

Phase I Projects

Title of Project: Microcomputer Data Management for Animal Resources

Principal Investigator: James L. Geer

Awardee Organization: Amitec
Community Health Services Building
933 South 19th Street
Birmingham, Alabama 35205

Telephone Number: (205) 933-5905

The goal of this project is to develop a comprehensive package of microcomputer software programs designed to perform a large variety of data processing procedures required for efficient management of animal resources supporting biomedical research. Phase I formed the intellectual and technical foundation for the entire program package, and demonstrated the feasibility and technical merit of the project by fully developing several selected component subsystem programs. The goal of Phase II will be the completion of all remaining subsystem programs, rigorous testing of the entire system, and enhancing the product to run in a multiuser environment using modern peripheral devices, with emphasis on security and password protection of the data base. Phase III, supported entirely by private capital, will involve software production, marketing, sales, and user support. This project is essential to assure commercial feasibility of software production for a highly restricted, limited market at a cost that will encourage wide application of this powerful technology.

Title of Project:	An Interactive Biomedical Image Processor/Analyzer
Principal Investigator:	William C. Bradley
Awardee Organization:	American Innovation, Inc. 1009 Urban Avenue Durham, North Carolina 27701
Telephone Number:	(919) 688-8466

Current morphometry and image analysis systems can be broadly divided into those that display an image and require the user to trace the points or lines considered significant, and those that apply complex algorithms to locate significant objects autonomously. The investigators see a need for an intermediate system in which the user could rapidly indicate the approximate location of significant objects and allow the system to apply a simpler restricted edge-finding algorithm to determine the exact line to use. Such a system would be much faster than "dumb" morphometry systems and much less costly than "intelligent" image analyzers that cost hundreds of thousands of dollars. By using a new VLSI microprocessor specialized for signal processing tasks, the investigators believe that a system of this type can be designed to sell for $15,000 to $20,000. This would bring powerful image processing technology within the reach of many more researchers.

Title of Project:	Culturing Amphibians for Biomedical Research
Principal Investigator:	Ronald L. Tremper
Awardee Organization:	Center for Reptile & Amphibian Propagation, Inc. 8166 East Shaw Avenue Clovis, California 93612
Telephone Number:	(209) 233-9222

Large numbers of research-quality amphibians are needed annually for biomedical research. Currently, there are seasonal shortages and inconsistent supplies of the bullfrog, Rana catesbiana, and axolotl, Ambystoma mexicanum. Through temperature manipulation and hormonal injection it will be shown that these amphibians can not only be cultured and conditioned in captivity to the extent needed, but that such an activity can be expanded and established as a profit-making private enterprise.

By developing a reliable method for keeping bullfrogs indoors through the winter months, one could increase the research in this area by as much as 25 percent since, for 3 months of the year, there are no wild-caught frogs available. Much of the work on these frogs is related to human health by way of cellular comparisions and developmental similarities. Frogs will be hibernated under water at 48° Fahrenheit, then gradually warmed and put through a 3-week conditioning program that includes antibiotic injections and training the frogs to eat laboratory mice so that their survival rate is greatly increased. This will prevent loss of data to the researcher.

Axolotl research involves many experiments on tissue regeneration, which has broad implications for and information about human cell activity. Researchers need normal wild-type salamanders which are in short supply, so that their eggs and larvae may be studied. By keeping a constant source of water at a temperature between 60° to 78° Fahrenheit, it will be possible to breed these research organisms year-round and in large enough numbers to meet the needs of the biomedical community.

Once the feasibilty of this work is established, a larger physical plant will be needed to house many new species of animals. A cost-efficient supply of quality animals would be realized.

Title of Project:	Design of N-Electrode LCEC for Biochemical Analysis
Principal Investigator:	Wayne R. Matson
Awardee Organization:	ESA, Inc. 45 Wiggins Avenue Bedford, Massachusetts 01730
Telephone Number:	(617) 275-0100

A need exists for better devices and new instruments to enhance diagnostics and for application to physiology and pharmacology. This project is studying the engineering variables and applications of coulometric electrodes in series for liquid chromatography electrochemical (LCEC) detector systems (n-electrode LCEC). Series coulometric electrodes assembled from existing commercial systems where n is 6-8 offer sub-picogram sensitivity, selectivities of up to 100,000, and the ability to do compound identification and verification by peak ratios on different electrodes. Six electrode assemblies allow the determination of catecholamines and metabolites in directly injected serum. The assemblies of existing equipment are, however, not optimized and are unnecessarily expensive.

Specialized n-electrode cells of two types will be constructed; four-electrode sample conditioning or "gate" cells and 6-10-electrode signal analysis or "array" cells. The cells will be evaluated for performance variables, that is, band spreading, back pressure, sensitivity, selectivity for the four-cell gate electrode, and resolution for the 6-10-cell array electrode. Preliminary applications for direct injection of biological samples for neurotransmitters will be run and compared with existing 6- and 8-cell series data, particularly for samples from patients with Alzheimer's disease. Detection of biochemical levels of enkephelins will also be tested. A second project covering application of this technique specifically to Alzheimer's disease is also being considered. It is expected that sensor arrays will be produced that have band-spreading compatible with microbore or fast LC columns, sensitivity of 200 femtogram or better for neurotransmitters, and resolution in the detector that will allow separation of coeluting peaks with 60 millivolts (mv) differences in their current-voltage curves. The Phase I efforts are devoted primarily to developing the specifications for later Phase II development.

Markets exist for such a product in the general research community, and larger clinical markets exist if the unique selectivity of the proposed sensors can be successfully applied to the diagnosis of particular diseases.

Title of Project:	Computerized Radio Inventory Location and Control System
Principal Investigator:	Eliezer Pasternak
Awardee Organization:	Here, Inc. 3360 Thomas Drive Palo Alto, California 94303
Telephone Number:	(314) 531-0138

This research project is intended to develop a technological solution to the problem of managing the location of inventory in an office, hospital, or research environment. The long-term objective is to develop and commercialize a computerized system that can locate automatically individual items of inventory in a building.

An object is located by attaching a special, digitally encoded electronic label to it. A computer connected to an electronic interrogator communicates with the labeled items and identifies their location.

The economic feasibility of this system is based on the availability of low-cost computer equipment and the development of a passive (without a battery), low-cost, complimentary metal oxide on silicone (CMOS) chip for the labels.

Phase I will involve the prototype development and experimentation of the critical elements of this technology, namely, the chip, the interrogator, and the wireless communication between them.

In Phase II, the entire system will be developed including the interrogator-to-computer interface and the computer software.

The health-related applications include maintenance of patient-care documents. Future applications of this technology can include drug inventory control, laboratory specimen identification, and entrance/exit control for authorized personnel.

Title of Project:	**Making Gel-Free Mass Spectrometer Photoplates**
Principal Investigator:	**Joseph I. Masters**
Awardee Organization:	Ionomet Corporation Box 222, 2 Oak Meadow Lincoln Center, Massachusetts 01773
Telephone Number:	(617) 259-0536

Vacuum-evaporated silver halide gel-free photoplates are needed in small quantities for health-related organic mass spectrometry. Although this detector has significant technical leverage in the bio-chemistry and biomedical fields, where it provides unique and unprecedented performance, its low volume precludes commercial applications. Since the risk of future unavailability is inappropriate, a project that will make a practical, small-scale, modestly priced instrument that will produce these photoplates is proposed. The investigators have the knowledge to perform this task, since they originated the plate and designed its production facility.

Phase I will examine technical and cost-related feasibility issues, including options for thickness control and plate handling under vacuum. Phase II will involve finalizing a design, building a prototype, and laying the foundation for production of this equipment. Where the proposed instrumentation primarily addresses a specific technical need rather than a commercial opportunity, its particular coating configuration offers commercial promise beyond the immediate needs of mass spectrometry. Once the product becomes commercially available, it has potential use in the semiconductor industry as a unique tool for high-throughput uniform coating of large silicon wafers with the high-resolution non-polymeric inorganic photoresists (similar to silver halide in terms of vacuum evaporation conditions) for printing large-scale integrated circuits.

Title of Project:	The First Immunoassay Method Practical for Office Use
Principal Investigator:	Myron J. Block
Awardee Organization:	ORD, Inc. P.O. Box 50 Nahant, Massachusetts 01908
Telephone Number:	(617) 592-3650

The long-term objective of this project is to develop a new immunoassay method for use in the dentist's and physician's office. The specific aim is to determine the accuracy of the interstitial volume correction in raw saliva. This method will use the evanescent wave on the surface of an optical fiber to optically separate bound from unbound antigen/antibody and to minimize the flourescent background of the specimen. The fiber is in raw specimen contained in a capillary tube, which minimizes specimen handling and sensitivity to specimen volume. It also corrects for interstitial volume. It will use only a few microliters of unprocessed specimen (for example, raw saliva or whole blood). The fluorescent tagged reagents will have a long shelf life. The instrument may be about the size of a pocket calculator. Possible assays will include hormones, drugs, and infectious agents.

It is expected that this method will make immunoassay practical for use in the dentist's and doctor's office. It will have an impact on the method of delivery of health care since there will be no need to wait for results from the lab, since the results will be available during the visit.

Title of Project:	**Machine-Reading Old Program Records: A New OCR Approach**
Principal Investigator:	**Peter C. Studt**
Awardee Organization:	**Sunol Sciences Corporation** **11887 Dublin Boulevard, S-B135** **Dublin, California 94568**
Telephone Number:	**(415) 828-5531**

Collation and distribution of information and data on experimental and clinical studies related to medical treatment is a valuable service provided by research centers. This information may be in the form of old program records or unformatted, handwritten notes that are awkward to store, retrieve, and transmit. A novel approach is proposed for the conversion of these records to computerized, digital formats. The proposed technique uses software control of input parameters, such as source illumination and sharpness of focus, to augment the optical character recognition (OCR) process. This approach is particularly adapted to the reading of old records, which may show irregularities in print contrast and legibility. In addition, this approach requires less computing power than conventional OCR techniques and can be implemented on a microcomputer.

The feasibility of this approach will be determined in Phase I, and supporting data for the Phase II prototype design will be collected. The commercial potential of the proposed optical reader is considerable in that relatively inexpensive devices could be developed. Thus, optical reading technology would be available to local information distribution centers such as libraries and schools, as well as to handicapped individuals.

Title of Project:	T-2000, Medical Information System
Principal Investigator:	Jaime N. Cadena
Awardee Organization:	Tobitron, Inc. Post Office Box 308 East Hampstead, New Hampshire 03826
Telephone Number:	(603) 329-5483

In Phase I of the project, the investigators intend to research and develop the T-2000, a medical information system that will produce instant real-time information that will project onto a monitor or, in other applications, supply written information through a printer. The device will consist of two major parts. The investigators intend to propose alternatives for a medium with which people can carry information about their medical histories in their wallet, or in necklace or bracelet form. The medical information will be contained within the chosen medium. The specific aim during the Phase I study is to take into consideration technical aspects of producing a functional prototype of the unit and the information disk, and to investigate indepth the human factors involved with such a system, such as legal, ethical, and medical issues.

The specific aim of the entire project is to manufacture the T-2000 Medical Information System and promote its international distribution and acceptance as a significant means of providing the population with a precise, cost-effective data system to communicate and process medical information and histories.

Title of Project:	**Tongue Activated Computer Control for the Handicapped**
Principal Investigator:	Daniel Fortune
Awardee Organization:	Zofcom Assistives 1148 Brace Avenue San Jose, California 95125
Telephone Number:	(408) 998-0933

Development of a tongue-activated controller will permit high-level paraplegics and quadraplegics rapid, voice-independent computer input and device control. Since tongue function closely resembles the fingers in sensitivity, quickness, and special awareness, the tongue is an ideal means of communication.

The goal is to design and construct a tongue-controlled device and to hook up this device to any suitable personal computer and processing packages.

In Phase I, the investigators will complete the incorporation of switches into a palatal splint and linkage with the personal computer, arriving at a working prototype. Phase II will involve extended human factors and user testing to develop a commercially acceptable product.

The intraoral palatal splint tongue-activated computer controller (TACC) gives limited-mobility handicapped people the ability to communicate with a computer data bank or to operate equipment with an alphanumeric keyboard. With the assistance of this device, handicapped individuals may regain control over their surroundings, or perhaps control their environment for the first time in their lives.

Phase II Projects

Title of Project:	Development of the U.S. Health Data System
Principal Investigator:	Daniel S. Levine
Awardee Organization:	Levine Associates, Inc. 11426 Rockville Pike, Suite 401 Rockville, Maryland 20852
Telephone Number:	(301) 984-3885

This research project will develop a user-friendly health statistics reporting system based on the extensive body of federally collected health data that is available and rarely used commercially. The data files will bring together data from many sources and create estimates of items not directly reported in, but implied by, the material in those sources, such as hospital costs by diagnostic related groups (DRG), so as to make this vital data available to the general public. The data base maintenance and statistics reporting will be implemented through a data base management system (DBMS). The resulting data set will be highly transportable so that it can be made available to potential users through secondary distribution channels, such as health provider association data systems. The data base will also be available on 9-track tape, and portions of it will be available in printed form in a data book. The basic system, though, will operate interactively. Consulting and training support will be provided. The tasks involved in completing this work are: data base design and preparation, selection of a DBMS and creation of the data base; development of reporting softare within the DBMS; system testing and refinement; and development of distribution and financing arrangements.

Title of Project:	Crystal Identification Sensor for PET Imaging
Principal Investigator:	Gerald Entine
Awardee Organization:	Radiation Monitoring Devices, Inc. 44 Hunt Street Watertown, Massachusetts 02172
Telephone Number:	(617) 926-1167

Positron Emission Tomography (PET) is a noninvasive medical imaging technique that provides a three-dimensional image of radio pharmaceuticals in the body. It has already yielded exciting results in the study of brain metabolism and can be applied to a large number of problems both in clinical diagnosis and fundamental research. The heart of the instrument is an array of gamma-ray detectors, which usually consists of bismuth germanate (BGO) crystals coupled to photomultiplier tubes. The size of the phototubes limits current PET performance.

A new idea that offers a practical solution is the use of a crystal identification sensor. One large phototube is coupled to a number of separate BGO crystals, each of which is identified by a solid-state photosensor.

The goal of this research project is to develop the technology of avalanche photodiodes so that they can be used in PET scanners. No other solid-state sensor combines the essential qualities of large area, internal gain, and room temperature operation. In Phase I, the dominant source of electronic noise was identified and techniques were developed to reduce it. The blue sensitivity has also been improved by careful control of the front surface structure. This has resulted in photodiodes that show great promise when coupled to BGO, demonstrating the feasibility of this detector scheme. In Phase II, the investigators plan to build on their success and to investigate the detailed construction of a PET detector assembly using the avalanche photodiode.

NATIONAL LIBRARY OF MEDICINE

Phase I Project

Title of Project:	Cancer Research Information-Exchange Bulletin
Principal Investigator:	Lucille F. Adamson
Awardee Organization:	Biomedical Literature Intelligence Services Post Office Box 2037 Corvallis, Oregon 97339
Telephone Number:	(503) 758-4260

This research will explore the feasibility of an innovative, networking approach to exchange of cancer research information not normally published (such as negative results). It will determine whether a bulletin to which readers contribute such items for publication will, during an initial grant-supported period of free distribution, attract sufficient readership and participation to become self-supporting.

Phase I of the project will include (1) assessment of the probable levels of subscriptions and contributions to the planned bulletin; (2) solicitation of suggestions for changes in the intended content; (3) production and distribution of 6 monthly issues of the bulletin; and (4) evaluation of the results and decision concerning continuation to Phase II of the project.

The bulletin would include the following sections: (1) Cancer Research Alerts; (2) Unpublished Research Results (chiefly negative results); (3) Research Suggestions and Questions; (4) Resources: Requests and Offers; (5) Editor's Contributions; (6) Network Feedback; and (7) Temporary Positions.

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Phase I Projects

Title of Project:	Electrochemical Sensor for Alcohol in Breath
Principal Investigator:	Myles A. Walsh
Awardee Organization:	Cape Cod Research, Inc. Post Office Box 600 Buzzards Bay, Massachusetts 02532
Telephone Number:	(617) 759-5911

This research explores the feasibility of using a novel electrochemical sensor for monitoring the alcohol content in breath. Successful demonstration during the Phase I effort of the proposed sensor's response, precision, accuracy, detectivity, life, and tolerance to interferences will lead to a Phase II project to develop a computerized instrument for the measurement of alcohol treatment compliance.

The proposed Phase II instrument would use the sensor developed in Phase I and would be capable of three functions. The patient would communicate with the microprocessor via a microphone and a liquid crystal display. The microphone would also contain the alcohol sensor so that the identity of the user as well as the user's breath alcohol level could be measured simultaneously. The patient would be asked to play games while speed and accuracy was being monitored. These data, along with the time and day, would be stored on tape for later analysis by the physician's computer.

The importance of the proposed research lies in the fact that only the lack of a portable, sensitive, rapidly responding and inexpensive alcohol sensor prevents the development of a wide range of commercial products, including a handheld ethanol detector for police inspections, a video game to check impairment as well as breath alcohol level, systems for preventing the operation of motor vehicles while under the influence, and instruments for public health research into alcohol abuse and treatment.

Title of Project:	Platelet Enzymes: Markers of Alcoholism or Alcohol Abuse
Principal Investigator:	Robert A. Anderson, Jr.
Awardee Organization:	Lohocla Corporation 2630 North Magnolia Street Chicago, Illinois 60614
Telephone Number:	(312) 871-1660

The goal of this project is to develop simple and reliable biochemical tests that can be used to identify individuals at risk for alcoholism, and/or to accurately indicate recent alcohol abuse. In Phase I, the feasibility of using platelet enzymes as such markers is being assessed. Preliminary studies have indicated that certain characteristics of platelet monoamine oxidase (MAO) activity (that is, sensitivity to inhibition by ethanol) and adenylate cyclase (AC) activity are altered in alcoholics as compared to control subjects. In the proposed studies, the differences will be confirmed in a larger population and reliable methods for platelet preparation and enzyme assay will be developed that will accentuate these differences. Enzyme activities in platelets obtained from alcoholics who have abstained from alcohol for various lengths of time will also be examined to determine whether observed changes in platelet enzyme activities result from exposure to ethanol, or are indicative of genetically determined differences between alcoholics and control subjects.

In Phase II, the chosen assay methods for MAO and AC activity will be streamlined for clinical use. The reversibility of enzyme changes will be further assessed, and enzyme activities in other psychiatric populations (for example, schizophrenics or patients with affective disorders), as well as in female alcoholics, will be examined to determine the specificity of these tests for alcoholism or alcohol abuse. The development of simple and reliable tests for diagnosing past alcohol abuse or a predisposition to abuse alcohol will provide for the physician: (1) a means of ascertaining an important contributing factor to major pathologic conditions; (2) a means of assessing patient compliance with instructions to terminate alcohol intake; and (3) a possible means of identifying individuals at risk for developing problems with alcohol in the future. Early identification can allow for earlier and more effective intervention in the pathology of alcoholism.

Title of Project:	Use of Autotimer in Alcohol and Drug Rehabilitation
Principal Investigator:	William B. Leaf
Awardee Organization:	Prototypes, Inc. 10449 Metropolitan Avenue Kensington, Maryland 20895
Telephone Number:	(301) 942-1731

This project is directed to the reduction of the morbidity and mortality associated with alcohol use, alcohol abuse, and alcoholism.

Problem drinkers, alcoholics, and other drug users present a major highway safety problem. Suspension of the driver's license is a frequently used penalty when these individuals are convicted of driving while impaired. Because the probability of being apprehended for driving without a license is very low, many offenders continue to drive despite revocation. To avoid interfering with the ability of the individual to earn a living, the court will often issue a restricted license that allows driving to and from work or while on the job, but not during evening hours when most alcohol-related accidents occur. Improved supervision of license restrictions could reduce the frequency with which offenders become involved in accidents.

This study is designed to determine whether an electromechanical device ("Autotimer") attached to the car of an offender can monitor driving to ensure that it conforms to the hours of the day set by the court. The cost-effectiveness of this monitoring system will be determined in relationship to the current practice of permitting unsupervised restricted licenses to be issued to drunk driving offenders.

NATIONAL INSTITUTE ON DRUG ABUSE

Phase I Project

Title of Project:	Monoclonal Antibodies and Immunoassays for Cannabinoids
Principal Investigator:	Harvey J. Brandwein
Awardee Organization:	Genetic Diagnostics Corporation 160 Community Drive Great Neck, New York 11021
Telephone Number:	(516) 487-4719

As marijuana use has continued to grow, the need for accurate and reliable means of measuring cannabinoid levels has become more urgent. The objective of this Phase I project is to develop such a cannabinoid assay that will be rapid, non-isotopic, and capable of being performed in a field setting. Specific goals for Phase I will be to generate murine monoclonal antibodies to tetrahydrocannabinol (THC) and to begin work on the development of a sensitive and versatile THC fluorescence immunoassay that will be faster, easier, and at least as sensitive as currrent radioimmunoassays, which can detect 10 nanograms per milliliter.

Monoclonal antibodies will be prepared against two different immunogens. A 5'-carboxy 9-THC-BSA conjugate, which has been generously provided by NIDA, will first be used. Subsequently, a conjugate will also be used that will be prepared via carboxy-methylation and carbodiimide coupling of the phenolic hydroxyl of 9-THC. Approximately characterized antibodies will be attached to β-galactosidase and used in a rapid solid-phase enzyme immunoassay using fluorogenic substrates. Such an assay system, when fully developed, will have significant commercial market, and will be useful for law enforcement agencies, the military, and other aspects of drug research programs.

Phase II Projects

Title of Project: Enzyme Immunoassay for Emergency Drug Screening

Principal Investigator: Peter N. Duquette

Awardee Organization: Bio-Metric Systems, Inc.
9932 West 74th Street
Eden Prairie, Minnesota 55344

Telephone Number: (612) 941-0080

Drug abuse with its potential for overdose poisonings, both intentional and accidental, is a major and rising health problem in the United States. Factors contributing to this rise are the rapid increase in the number of prescriptions written for drugs having abuse potential (for example, analgesics and psychopharmacologic agents) and the rapid rise in the national geriatric population (which consumes large numbers of prescription drugs). Health care professionals have long recognized the need for rapid analytical methods for determining in an emergency situation which class of drug or drugs is present.

Numerous methods are available for determining drug levels in biological fluids but all require diagnosis in a laboratory. Most of the available assays require trained personnel and expensive equipment, and are slow in determining the drug present. Radioimmunoassay procedures produce the additional problem of radioactive waste disposal, which is currently, and increasingly will become a major problem in the future.

Phase I results provided a basic proof-of-concept for the development of a strip enzyme immunoassay that will be useful in emergency situations for determining which class of drug or drugs was taken in excess. The assay is simple, fast (fewer than 6 minutes), noninstrumental, and thus easily portable by emergency personnel at the scene of the suspected overdose. Further development of this assay will allow the determination of the drug class and thus allow for general supportive measures before the patient's arrival at medical facilities.

Title of Project:	Drug Abuse Assessment in Industry
Principal Investigator:	Royer F. Cook
Awardee Organization:	RCI 11739 Bowman Green Drive Reston, Virginia 22090
Telephone Number:	(703) 471-6881

The goal of this research and development project is to develop innovative techniques for assessing drug and alcohol abuse in the industry. The assessment technique will be useful for: (1) needs assessment, estimating the prevalence and nature of drug and alcohol abuse among employees; (2) identification of individuals with drug or alcohol problems; and (3) monitoring and evaluation of drug and alcohol program efforts. During Phase I, several techniques were identified that showed promise of commercial potential.

During Phase II, a series of research/validation studies will be conducted at industrial sites for developing and testing (1) survey interview techniques, (2) employee records analysis, and (3) self-identification techniques (computerized self-assessment methods). The use of blood chemistry analysis will also be explored. Both criterion validation and convergent validation studies will be conducted, leading to a set of reliable and valid techniques, and culminating in their preparation for commercial application.

NATIONAL INSTITUTE OF MENTAL HEALTH

Phase I Projects

Title of Project:	Software for Guiding and Assessing Family Interaction
Principal Investigator:	Elaine T. Carella
Awardee Organization:	ASIP, Inc. 62 Yankee Peddler Path Madison, Connecticut 06443
Telephone Number:	(203) 245-7580

Board games designed to train parents, children, and married couples in problem-solving, communication, and negotiation skills have been found effective as therapeutic, preventive, and basic information gathering devices.

Phase I of this project has three specific aims: (1) develop three interactive computer software packages that will retain the therapeutic value of the original board games; (2) include in these packages the capacity for online assessment of family problem solving; and (3) test the short-term effectiveness of these packages in three multiple-baseline single-case experimental studies with three groups of eight distressed families.

The long-term objectives of the project are to develop three software packages that can be used as a central component of marital or family therapy with distressed families, for prevention purposes with high-risk families, and for health promotion with non-distressed families. The software will permit online continuous recording of the flow of interaction between therapist (software) and group, and among group members. This feature will contribute to basic knowledge about mechanisms of family problem solving.

Title of Project:	Computer Software for Adverse Health Events
Principal Investigator:	Dean J. Clyde
Awardee Organization:	Clyde Computing Service Post Office Box 1086 Key Largo, Florida 33037
Telephone Number:	(305) 524-0776

The SAFTEE-GI and SAFTEE-SI forms were developed to collect information on adverse health events occurring during clinical trials. Investigators are beginning to record data with these forms. A system is needed for entering information from the forms into a computer, storing it on magnetic media, and retrieving and summarizing the information in meaningful ways.

The investigators propose to develop computer software that will accept adverse event data rapidly and accurately from a keyboard, store the information efficiently on diskettes or fixed disks, and make it easy for scientists to retrieve and analyze the data whenever desired.

During Phase I the investigators will confer with developers and users of the SAFTEE forms, select suitable computer hardware, draw up detailed specifications for the required programs, and write the programs. The complete hardware and software system will be tested and demonstrated to users. As a result of their comments, the programs will be modified and demonstrated again. The researchers will make the software available to any investigators who wish to use it.

During Phase II the investigators expect to publish a user's manual and offer short training courses for computer operators. As users gain knowledge, they will think of new ways to analyze adverse event data. Enhancements will be added to the software to meet their needs.

Title of Project:	Small Computer Applications in Mental Health Centers
Principal Investigator:	H. Ned Seelye
Awardee Organization:	International Resource Development, Inc. Post Office Box 930 Lagrange, Illinois 60525
Telephone Number:	(312) 579-9050

The recent explosion in microcomputer technology offers time-saving and cost-effective ways for community mental health centers (CMHC) to computerize their routine operations, but CMHC staff need help in using small computers effectively. The biggest impediment to expanded computerization is the lack of available software designed to meet the special needs of CMHC's.

The aims of this project are to: (1) present a descriptive matrix of existing mini- and microcomputer software designed to respond to the information system needs of CMHC's and (2) determine the feasibility of adapting inexpensive, generic, data base management software programs to handle the majority of the information needs, identified through a literature review, will be verified through a sample of Chicago-area CMHC's. The search for appropriate software includes polling every nth CMHC from a national director, as well as directly contacting vendors. Generic data base management software will be described (in terms relevant to CMHC applications) from publishers' specifications and from hands-on experience.

The final report will assess the feasibility of developing (in Phase II) records templates that allow CMHC's to use data base management programs to handle the information system needs of most of their routine administrative and clinical operations. The investigators also will assess the feasibility of developing new software programs.

Phase II Projects

Title of Project:	Microprocessor-Based Psychometric Testing Device
Principal Investigator:	William C. Bradley
Awardee Organization:	American Innovation, Inc. 1009 Urban Avenue Durham, North Carolina 27701
Telephone Number:	(919) 688-8466

Advances in microcomputers and video storage technology have made major improvements in systems for administering psychometric tests possible. A prototype of a microprocessor-controlled psychometric testing device that uses an inexpensive consumer model video disk recorder to store both images and computer programs was built in Phase I of this project. The system is designed to generate tests requiring text or computer graphics under the control of programs read off the video disk, and to present tests requiring detailed images by positioning the disk and displaying a disk frame in freeze-frame format. Essentially all tests in common use could be administered with this system; a single disk could store a very large number of tests. This system would also make possible new tests using moving graphics or video as a stimuli and recording the time and location of light pen responses.

In Phase II the hardware will be readied for mass production, the first video disk of the tests will be mastered, and the tests will be revalidated in their new format.

Title of Project:	Brain Vasculature Digital Tomosynthesis Hardware Level
Principal Investigator:	Robert M. Moore
Awardee Organization:	Kermath Manufacturing Corporation 2251 Dabney Road Richmond, Virginia 23230
Telephone Number:	(804) 254-4505

In this project the investigators are developing clinical positioning devices to further the development of digital tomosynthesis applications emphasizing brain vasculature studies. In collaboration with the Departments of Radiology at the University of Mississippi and the University of Virginia, the investigators propose to use experience gained from the previous design of conventional L-C positioning devices that employed conventional tomographic capabilities, and L-C positioning devices that support digital vascular imaging (DVI) devices to producing the subject hardware.

Two DVI systems which will be used with the L-C positioning devices have been designed and constructed at the University of Mississippi and the University of Virginia which will serve as clinical evaluation sites. These DVI systems will employ tomosynthesis applications (a method of tomography using a number of fixed exposures and manipulation by an image processor).

While literature supports the need for digital tomography, the only available positioning hardware is of test-bench variety and not suitable for clinical use. The investigators propose to develop and furnish clinical hardware to complement the required DVI motion and attitude requirements.

Title of Project:	Microcomputer Based Rehabilitation
Principal Investigator:	Ruth A. Maulucci
Awardee Organization:	Moco, Inc. 5 Champlain Drive Hudson, Massachusetts 01749
Telephone Number:	(617) 562-9000

The specific aim of this research is to produce a microprocessor-based rehabilitation system that can be used to enhance functional recovery. The system is a comprehensive work station in which the patient can exercise a variety of motor and cognitive skills in order to restore the basic processes that underlie purposeful behavior.

To achieve this goal, there are three major areas of investigation underway. First, a number of innovative input devices are addressed for training. Second, an extensive set of training tasks based on modern structure is being defined in order to allow the rehabilitation professional, with no knowledge of programming, to generate entirely new training tasks involving any of the available sensors.

The resulting rehabilitation workstation will be reasonably priced for individuals. It will make it possible for a limited number of therapists to serve a larger group of patients by allowing a normal patient/therapist session to be expanded into self-directed or family-directed group therapy.

CENTERS FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Phase I Projects

Title of Project:	Instrument for Worksite Evaluation of Hearing Protection
Principal Investigator:	Dominic W. Huges
Awardee Organization:	Med Data Associates, Inc. 6303 Southwest 40th Avenue Portland, Oregon 97221
Telephone Number:	(503) 232-8107

The long-term objective of this project is the prevention of noise-induced hearing loss through development of an instrument for worksite measurement of the true effectiveness of insert-type hearing protection devices (HPD's) as worn.

The specific aims are to: (1) determine an optimum suprathreshold method for measuring, in high ambient noise, attenuation of HPD's; (2) incorporate this method into the prototype instrument for operation at the worksite by unsophisticated testing personnel; and (3) establish the instrument's technical merit and gather performance data for Phase II development of a marketable test instrument.

The investigators' methodology is to: (1) develop computerized laboratory instrumentation for presenting diverse auditory stimuli and recording subject responses; (2) develop program instrumentation to provide various suprathreshold tests for evaluating HPD's as worn; (3) evaluate tests for degree of difficulty, validity, reliability, and test integrity in environmental noise; (4) build a prototype portable field test instrument incorporating the most satisfactory test method and instrument configuration; (5) confirm in the laboratory the validity of the results obtained with the prototype instrument in comparison with results concurrently obtained by standard methods and instrumentation; and (6) conduct initial field testing of the prototype instrument to establish its feasibility and acceptability at the worksite.

By far, the most common source of communicative disorders below age 60 is noise-induced hearing loss. Incorrectly fitted HPD's are placing a high percentage of workers exposed to noise at risk; thus, a need exists for a means of measuring the true attenuation of these devices in the field.

The final instrument could be used in approximately 59,000 United States industrial plants.

Title of Project:	Respiratory Hazard Control for Swine Confinement Buildings
Principal Investigator:	Dorrance G. Haught
Awardee Organization:	Yoder, Inc. Kalona, Indiana 52247
Telephone Number:	(319) 683-2427

University consultants have documented through research conducted over the past 7 years the emergence of an important new respiratory disease hazard to the agricultural population. Seventy to 90 percent of the estimated one-half to one million workers in swine confinement structures experience respiratory symptoms and 55 percent experience chronic bronchitis. At least 14 workers have died suddenly from acute respiratory distress and systemic toxicosis.

The ultimate goal of this project is to prevent respiratory disease in swine confinement workers by improving the work environment though improved work practices and through the application of cost-effective industrial hygiene and engineering controls.

The investigators will outfit a recently constructed confinement facility with instruments and initiate studies on the relationship between controllable environmental factors and environmental concentrations of ammonia, hydrogen sulfide, methane, carbon dioxide, and aerosols. The investigators will install environmental monitoring devices, then evaluate the costs and environmental effects of the types of ventilation system, the ventilation rate, production practices, and the physical and chemical makeup of the feed. These preliminary Phase I studies anticipate a larger series of studies that could result in the development of marketable environmental control technologies or principles that will economically improve the occupational health of a large and growing segment of the farming population.

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

Phase I Project

Title of Project:	New Sterilization Process for Heat Sensitive Foods
Principal Investigator:	J. Morris Binder
Awardee Organization:	Tone Brothers, Inc. Post Office Box AA Des Moines, Indiana 50301
Telephone Number:	(515) 262-9721

The investigators propose to design and develop an alternative process for sterilizing heat-sensitive free-flowing food products, such as spices, which will replace conventional ethylene-oxide sterilization methods. The ethylene-oxide method creates exposure hazards to employees and potential residual combination products that can be unnacceptable in certain foods.

In Phase I, the feasibility of a new process using heat, pressure, and a novel quenching process will be determined for whole pepper. Operating parameters such as temperature, exposure time, pressure, microbial reduction, and volative oil retention will be determined using a pilot-scale system.

A cryogenic quenching process with temperatures down to -300 degrees Fahrenheit is expected to have a synergistic effect on both microbial reduction and quality retention.

The commercial application and the health benefits of an improved hazard-free sterilization process are very significant, and in Phase II, extension and testing with other heat-sensitive food materials will be undertaken.

HEALTH RESOURCES AND SERVICES ADMINISTRATION

HEALTH RESOURCES AND SERVICES ADMINISTRATION

Phase I Project

Title of Project:	Preparation of Workbook for Children of ESRD Patients
Principal Investigator:	Robert D. Bruce
Awardee Organization:	Hoover Keith & Bruce Inc. 9730 Town Park, Suite 108 Houston, Texas 77036
Telephone Number:	(713) 496-9876

The long-term objectives of this project are to develop child-oriented literature to assist children in dealing with emotionally disturbing events, such as hospitalization and death. Because of the great need for literature to assist children whose parents have end-stage renal disease (ESRD), the specific aim for Phase I is to prepare materials for these children. There are over 100,000 children who have a parent with ESRD. Current studies show that these children develop depressive and hypochondriacal Minnesota Multi-Phasic Inventory (MMPI) patterns and pseudomature behavior, and have latent aggressive feelings toward the sick parent. The investigators propose to develop a workbook, test the workbook on local children with ESRD parents, modify the workbook based on the response from the children, and publish it during Phase I. The workbook will be developed with the assistance of dialysis centers and professionals including a child psychiatrist, a social worker, a renal nurse, medical writers, and an illustrator, and will be oriented toward one of the child developmental stages. At the conclusion of Phase I, the investigators will identify other medically related areas that can benefit from similar child-oriented literature, and will propose to develop materials for these areas during Phase II. Also in Phase II, workbooks on ESRD for other child development stages will be prepared.

OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

NATIONAL CENTER FOR HEALTH SERVICES RESEARCH

Phase I Project

Title of Project:	Software Templates for Home Health Agency Case Management Information Systems
Principal Investigator:	Susan Stoddard
Awardee Organization:	Berkeley Planning Associates 3200 Adeline Street Berkeley, California 94703
Telephone Number:	(415) 652-0999

Home health agencies (HHA's) have a number of case management tasks that can be accomplished most efficiently through modern computer information systems: client tracking, service reporting, and expenditure records. However, only a few HHA's have the ability to develop their own tailored computer programs and build systems. The investigators propose to select a base microcomputer software package from commercially available data base management or integrated spreadsheet software, and develop, test, and package a template or templates that allow easy HHA user access to the range of information-handling capabilities of the new software and microcomputers. Templates would be designed to allow for input of defined client, service, vendor, and funds information; creation of client, client service, vendor, and service definition files; and three types of output: screen displays, routine pre-programmed reports, and ad hoc inquiry. The product would also be useful in improving the quality of HHA reporting to the Health Care Financing Administration.

OFFICE OF ADOLESCENT PREGNANCY PROGRAMS

Phase I Project

Title of Project:	Development of an Illustrative Microcomputer Data Archive
Principal Investigator:	Josefina J. Card
Awardee Organization:	Sociometrics Corporation 3191 Cowper Street Palo Alto, California 94306
Telephone Number:	(415) 595-2216

Recent developments in electronic technology have the potential of radically changing both the manner in which social science data are analyzed and the degree to which these data are used. This project will take advantage of the dramatic decreases in cost and increases in accessibility that will be brought about by the imminent implementation on a personal computer of a major mainframe data analysis package (SPSS). The investigators will establish on a personal computer an easily accessible, state-of-the-art data archive on teenage family life, sexuality, pregnancy, contraceptive use, and childbearing. Because the principal investigator is already developing such an archive for mainframe use, the personal computer version can be established for a fraction of the investment already made in data base identification, selection, acquisition, processing, and documentation.

This project will proceed in three phases: pilot implementation (Phase I), full implementation (Phase II), and distribution (Phase III). Phase I will explore the feasibility, utility, and cost of transforming the mainframe computer archive's data and documentation into products suitable for microcomputer use and analysis. Phase I will also evaluate the strengths and limitations of a microcomputer-based data archive relative to its mainframe twin. If warranted by results from Phase I, the complete archive--consisting of a set of 50 to 60 important data bases and their associated documentation, accompanied by sample exercises for educational use--will be established. In Phase III the archive's products will be marketed to data depositories, university libraries, college professors, researchers, and other professionals (such as practitioners and policymakers) interested in adolescent and youth-development issues. Insights gained from the study should be transferable to the archiving and analysis of data sets dealing with substantive topics other than teenage sexuality and pregnancy. Future work may explore these possibilities.

HEALTH CARE FINANCING ADMINISTRATION

HEALTH CARE FINANCING ADMINISTRATION

Phase I Projects

Title of Project:	Long Term Care Client Targeting Manual
Principal Investigator:	Brenda Haskins
Awardee Organization:	Berkeley Planning Associates 3200 Adeline Street Berkeley, California 94703
Telephone Number:	(415) 652-0999

The purpose of this project is to develop and market an inexpensive, brief, and easily usable client targeting manual for providers of long-term care to enhance decision-making concerning service to the frail aged. The manual will be based on empirical findings from a recent national evaluation of 13 community-oriented long-term care demonstration projects. The manual would disseminate recent selected data and methods for appropriately targeting long-term care services to elderly people who, except for a service intervention, would likely enter an institution. These findings about long-term care client targeting will encourage savings in public (especially Medicaid) dollars by helping service providers target and allocate services to those who are truly at risk of institutionalization. The client targeting manual will serve a second purpose: dissemination of recent research and demonstration findings in long-term care. The manual will also instruct service providers in recent long-term care case management practices, with the aim of encouraging appropriate noninstitutional alternatives to long-term care.

Title of Project:	A Voucher Insurance Plan to Mobilize Volunteer Support Among the Elderly
Principal Investigator:	Stuart P. Hanson
Awardee Organization:	Berkeley Planning Associates 3200 Adeline Street Berkeley, California 94703
Telephone Number:	(415) 652-0999

This project is to develop a Voucher Insurance Plan (VIP) to mobilize volunteer support among the elderly Medicare-eligible membership of social clubs, trade unions, churches, and retirement communities. The plan is designed to operate as an insurance plan. For each unit of service performed, the volunteer will receive a voucher entitling him or her to an equivalent amount of service. The voucher may be exchanged and even cashed out. A professional health care assessment and training component will be added to support the altruistic/self-interested volunteer behavior.

The basic objective of Phase I is to derive empirically sound maximum likelihood estimates, using conditional analysis of VIP components such as membership dues, kinds and values of various services, cashing-out values, and voucher circulation patterns. These results will form the empirical base of VIP policy and procedures that will be extensively tested during Phase II and marketed to voluntary organizations with geographically stable elderly populations during Phase III. San Francisco Home Health Service, with its 4,000-member Senior Center, will cooperate in all phases.

Title of Project:	The Consumer as a Partner in Medical Cost Containment
Principal Investigator:	Ellen Wagman
Awardee Organization:	Keneko Communications, Inc. 1700 Mission Street Suite 203 Santa Cruz, California 95060
Telephone Number:	(408) 429-9825

The investigators in Phase I of this project will establish the feasibility of and preparation for conducting an experiment on health care cost containment through a program of education and motivation of the medical consumer. The project will include the review, pretesting, and revision of a consumer guide to cost-efficient quality medical care. In addition, the project will involve the solicitation/commitment of nine San Francisco Bay Area corporations to serve as test sites; the development of test measures; the development and testing of two types of employee training programs; and an examination of baseline data on health care costs at the nine sites.

Successful accomplishment of these activities will complete the groundwork for the implementation of the 2-year health care cost containment experiment proposed as Phase II. The Phase II experiment will involve employees at nine corporate sites who will participate in one of three groups: (1) an untreated control group, (2) an experimental group given information and training about health care cost containment, and (3) an experimental group given this information and also a fiscal incentive contingent on successful adoption of the recommended cost containment strategies.

Material costs and self-report measures of medical activities will be collected and monitored for 1 year after the implementation of the interventions. Pre- and post-data will be tabulated to assess the effectiveness of the proposed interventions on actual medical costs, and qualitative reports will further assess their merit.

Title of Project:	Develop Management Techniques to Reduce Home Health Costs Using a Shared Aide System
Principal Investigator:	Lee Van den Bos
Awardee Organization:	HCR 1605 T Street, Northwest Washington, D.C. 20009
Telephone Number:	(716) 461-3580

This project assesses the feasibility of developing a programmed instruction management guide on the shared aide system for managing delivery of home health services. It is being carried out by analyzing the current management of four shared aide packages in Monroe County, New York. If the study shows that it is feasible to replicate the experience with the shared aide system, then it will be possible to develop a programmed instruction management guide that can be sold to home health agencies and local governments. The guide will teach them how to implement the system to serve their clients. Preliminary operation of the shared aide system showed that it substantially reduced the cost of home health services while maintaining or improving the quality of care provided.

OFFICE OF HUMAN DEVELOPMENT SERVICES

OFFICE OF HUMAN DEVELOPMENT SERVICES

Phase I Projects

Title of Project:	Exploration of Marketing Employment Goals to Private Sector
Principal Investigator:	Claude High
Awardee Organization:	Action Management Corporation Consulting Division 712 Metropolitan Building 432 North Saginaw Flint, Michigan 48502
Telephone Number:	(313) 234-2828

The objectives of this project are to review current incentives offered business for its involvement with the target population; research effective methods of providing incentives to business; examine alternatives that increase private sector involvement; and study various marketing techniques to improve presentation of benefit packages to the private sector, for example, savings, cost cutting, and profit margins.

This project will be conducted by extensively researching various publications, periodicals, and government documents, through contact with the Michigan Department of Commerce and local economic development and planning units, and by reviewing and conducting surveys on attractive benefits to small businesses. Data from surveys will be correlated into a recommended approach for achieving effective marketing of incentives.

It is anticipated that the project will result in identifying additional incentives and benefits to attract business involvement in employing specific target groups. Additional business involvement should result in a decrease in barriers and an increase in employment opportunities for the target population.

The commercial application of the research will improve trade and commerce between government and business. Government will receive popular appeal for its programs and increased placement of the target population, while business will receive financial gains such as tax credits, reimbursements, and ordinance changes.

Title of Project:	The Marketing of Devices for the Developmentally Disabled Which Will Remove Certain Physical Barriers to Employment
Principal Investigator:	Cristobal S. Berry-Caban
Awardee Organization:	Atlantic Resources Corporation Post Office Box 3322 Reston, Virginia 22090
Telephone Number:	Unlisted

This project proposes to assist the sponsoring agency in the removing of barriers to employment of the developmentally disabled (DD). At the conclusion of the project, the agency and inventors of devices to assist the DD population will have access to a computer data bank that will identify the DD population that could benefit from a particular device. The specific industry barriers affected will also be addressed in the data bank.

To accomplish the goals of this project, the investigators will reinterpret the data gathered by the sponsoring agency in its National Health Interview Survey (HIS) and the Home Health Care Supplement (HHCS) to derive device-related data. The Electronic Industries Foundation (EIF) has agreed to act as a conduit for device information and as a link to the inventor and technological community.

Given the results of the project, an inventor or investor can match the barrier-removal characteristics of a device with the potential DD user population to determine market size and location and to predict costs and benefits for DD and industry groups.

The emerging high technology era for the United States will inevitably produce more and more ideas and systems to aid the developmentally disabled. The investigators feel this project will result in a commercially viable system from which subscribers and the agency can receive highly cost-effective benefits.

Title of Project:	Innovative Method to Remove Barriers and Train Blind Persons in Becoming Computer Programmers
Principal Investigator:	Carl Schleicher
Awardee Organization:	Center for Preventive Therapy and Rehabilitation, Inc. 1315 Apple Avenue Silver Spring, Maryland 20910
Telephone Number:	(301) 882-4000

The purpose of this project is to provide a method to remove barriers that hinder or prevent the employment of blind persons. An innovative method, called the Lozanov Learning System, is proposed to help train blind persons to become computer programmers and operators of automated equipment. Experiments with this method have proven that blind persons respond well to this auditory-based teaching system and could retain high amounts of rote material required in computer programming. The investigators plan to set up such a program in association with a computer learning school to provide on a commercial basis an effective, low-cost, accelerated and stress-free computer training program for blind persons. Such a program does not now exist, and this program, once validated here, could be applied on a national basis through the affiliated Lozanov Learning Centers.

Title of Project:	Analysis of Prior Study Results on Employment Problems in America
Principal Investigator:	W.J. Tigner
Awardee Organization:	Four J and Associates Research and Development Section 616 Treehaven Drive Birmingham, Alabama 35214
Telephone Number:	(205) 798-4642

The objective of this project is to demonstrate the feasibility of conducting a historical search of the employment literature to identify all studies dealing with the employment problem in the United States. The studies will be cataloged and a systematic analysis of the results of each study will be combined into a cross-referenced, indexed, and tabulated abstract on the employment problem. The abstract will provide a ready reference guide to Government, industry, researchers, and the general public in identifying successful and replicable techniques and models. The grantee's previous research in employment matters, coupled with events in the literature, has shown that there is a need for a systematic analysis that could be packaged into polished form for dissemination to the private sector. Ferman (1966) recommended that priority be given to establishing a clearing house for equal employment studies, and to recording past, present, and anticipated employment studies. This project proposes to advance that objective and to fill the void in the literature in this area.

Title of Project:	Job Creation Using Telecommuter Concepts
Principal Investigator:	Gail Gibson-Hunt
Awardee Organization:	Gibson-Hunt Associates, Ltd. Suite 700 1331 H Street Washington, DC 20005
Telephone Number:	(202) 737-5007

The purpose of this project is to assess the feasibility of two forms of targeted job creation, both of which employ telecommuter concepts. Jobs that can be done from the home using a computer or computer terminal with appropriate communications hardware and software are the focus of this project.

The target groups are one or more of the following: physically handicapped persons, welfare recipients, and the elderly. Each of these groups suffers in varying degrees from barriers to their employment (for example, need for special equipment, transportation limitations, need for part-time employment) that can be alleviated or eliminated through the appropriate use of technology.

To accomplish project objectives, the following tasks will be performed: (1) review prior research; (2) identify required characteristics of target populations and specify training requirements; (3) perform a market analysis; (4) develop business plans; and (5) present Phase I findings and recommendations.

The results of this project will be a feasibility assessment of the following two telecommuter employment possibilities: (1) word processing jobs with large private-sector firms that are highly automated; and (2) creation and staffing of a company that provides word processing support to small businesses that cannot afford their own word processors.

Either the method or the word processing support company could be franchised commercially.

Title of Project:	Commercial Program for Enhancing Long-Term Employment for Minority and Disadvantaged Employees
Principal Investigator:	Thomas K. Tulk
Awardee Organization:	Quantitative Services, Inc. Post Office Box 5276 Arapahoe County Englewood, Colorado 80155
Telephone Number:	(303) 796-9084

The purpose of this project is to develop a commercial program to increase the likelihood that a minority or disadvantaged employee will remain employed. Often due to cultural differences and skill levels, employment opportunities for minorities and disadvantaged persons are limited to menial jobs providing low satisfaction and sense of worth. Thus, high employment turnover rates occur.

The program developed by this project communicates the advantages of remaining employed and the opportunities for a beneficial career path. Research will be conducted on the primary reasons why these employees quit their jobs, quantifies the corporate administrative costs associated with high turnover rates, and develops a marketable program linking corporate employment strategies with the specific needs of minorities and disadvantaged groups. The program uses seminars and orientation sessions as the primary vehicles for communicating with both the employer and employees. Topics of the seminar modules are based on the results of the research.

The program reduces personnel costs and has a national market in both private and public employees. Techniques for targeting corporate clients and preliminary marketing strategy will be developed to verify the commercial viability of the program.

Title of Project:	Involving the Private Sector in Cooperative Development With Tribal Businesses
Principal Investigator:	Andre Dumont
Awardee Organization:	Southern Sandoval Investments, Ltd. Star Route, Box 37 Bernalillo, New Mexico 87004
Telephone Number:	(505) 867-3301

This project will examine the benefits to established businesses in working with tribally owned, for-profit entities to develop reservation enterprises. It will also study the benefits to Indian tribes in working cooperatively with the private sector. Finally, it will demonstrate a model for tribal/private sector cooperation in reservation resource development. This will be done by approaching corporate senior management to participate in a joint effort to share skills and methods with tribal decision makers at Santa Ana Pueblo in central New Mexico.

The product of the research will be a package of information on the mutual benefits of tribal/private sector cooperation and a case study of how this cooperation can work in the real world of business enterprise. There are two clear opportunities for commercial application of the research products of this project. The most obvious will be the cooperative development between the tribal corporation and the private sector partner that will be identified in Phase I. The longer range significance of the work will be in the precedent set by the joint effort and the knowledge that will be gained. This information will be marketed to Indian tribes and private businesses throughout the nation.

Title of Project:	Community Approach to Soiving Employment Problems
Principal Investigator:	Pamela Zoe Toconis
Awardee Organization:	Toconis & Associates, Personnel Service 470 Main Street Merced, California 95340
Telephone Number:	(209) 384-1555

The objective of this project is to create a long-range community-based mechanism for dealing with various employment problems in Merced County. The procedure will be designed so that it may be used as a model for other communities.

The initial step is to survey personnel directors and business executives to identify Merced County employment problems and potential solutions. A permanent volunteer task force of personnel executives and representatives of appropriate government agencies would be established. The task force would review survey data, make recommendations, and become an ongoing committee and sounding board for dealing with county-wide employment problems. The successful efforts of the task force would result in increased employment in Merced County, improve the quality of employment in the county, raise the qualifications of the local labor pool, and provide improved communication and coordination among local employees and employment resources.

Commercial applications would include: (1) creation of a central source of information on varied employment/personnel issues and (2) development of a local community training center for clerical training, employment workshops, management training, and possibly other trade school training.

Phase II Projects

Title of Project:	Aiding Aged Through Information Dissemination: Captures on Telephone Tapes Helpful Data on Devices
Principal Investigator:	Leonard A. Blackshear
Awardee Organization:	Associated Enterprise Development, Inc. 1623 Forest Drive, Suite 302 Annapolis, Maryland 21403
Telephone Number:	(301) 858-5585

In Phase I this project has demonstrated that hundreds of aids, devices, and procedures can be identified that will make it easier for the elderly and physically impaired to care for themselves, or be cared for.

In Phase II both data and technology will be developed to disseminate the information through a nationwide system. The "Aidline" will assist those who have a need for an aid or device, or those who care for the disabled, to identify the necessary aids, devices, and procedures without cost, simply by dialing a local telephone number. The system will be regionally sponsored with a sponsor's message (of twenty to thirty seconds) at the beginning of each tape. Sponsors may be health care providers, rehabilitation organizations, device manufacturers, pharmaceutical and hospital equipment manufacturers, organizations serving the elderly, existing health-related telephone tape technology systems, and others. The Aidline system will be made known by repeated publicity and by brochures giving simple instructions and listing all tapes by number. The sponsors will be individually identified with each call through the use of an access code or other identifying tape number prefix or suffix.

Title of Project:	Development of Integrated Management System for Small Providers Using Microcomputers and User Friendly Software
Principal Investigator:	Joseph A. Doucette, Jr.
Awardee Organization:	Computer Consulting and Programming Associates 7553 Canal Plaza Portland, Maine 04112
Telephone Number:	(207) 774-8242

This project establishes a directory that has a twofold purpose: (1) providing a useful source of information to all human service agencies that are interested in the computerization of their agencies, and (2) establishing human services as a viable market for software vendors and serving as a focus for their sales efforts.

The directory will contain four major sections:

1. Human Service Agency User Reviews: This will consist of reviews of computer software packages that are being used by agencies.

2. Software Vendor List of Products: The information in this section will be concerned with the features, capabilities, and requirements of the software products which would be most helpful to human service agencies.

3. Hands-on Detailed Review of Several Software Products: The most popular and innovative projects will be tested extensively by the grantee staff, rated, and compared to other existing products.

4. Suggested Hardware Configurations with Related Costs: Samples of total installations of microcomputer systems will be given along with the complete costs of acquiring such systems. This section will also note trends and techniques regarding computer system acquisition.

Title of Project:	A Tool for the Management of Human Services Provider Agencies to Monitor Performance, Assess Efficiency, and Provide Opportunities for Cost-Effective Improvement
Principal Investigator:	Bill B. Benton
Awardee Organization:	Urban Systems Research and Engineering, Inc. 1120 19th Street, Suite 600 Washington, District of Columbia 20036
Telephone Number:	(202) 293-3240

The purpose of this project is to develop a tool by which the performance of human service provider agencies may be assessed, opportunities for cost-effective improvement identified, and the best practices of provider agencies documented for replication in other settings.

Based on consultations with human service managers and a review of the literature in a number of fields, the investigators have developed and pretested an instrument that captures key dimensions of an agency's performance in a form that permits comparison with other agencies, with the same agency over time, in relation to established standards and norms, and against goals and objectives established by the agency.

During Phase II the grantee will expand the number of test sites for the instrument developed in Phase I. Additional Phase II activities include refining the instrument, expanding the demonstration, and evaluating the product's commercial value for Phase III.

SOCIAL SECURITY ADMINISTRATION and the
OFFICE OF THE ASSISTANT SECRETARY
FOR PLANNING AND EVALUATION

SOCIAL SECURITY ADMINISTRATION and the
OFFICE OF THE ASSISTANT SECRETARY FOR PLANNING AND EVALUATION

Phase II Project

Title of Project:	Establishing an Enterprise to Market the Products of Work Activity Centers to Consumers: Testing and Development
Principal Investigator:	Francis Kvidahl
Awardee Organization:	Human Services Group, Inc. Work Center Marketing Services 120 Milk Street, Eighth Floor Boston, Massachusetts 02109
Telephone Number:	(617) 542-1812

The grantee organization is a marketing cooperative whose objective is to increase the sales of products produced by work activity centers (WAC's) employing developmentally disabled persons. It has been shown that disabled workers feel more a part of the traditional work force and experience an increase in their sense of self-worth when earning an income from real work rather than "simulated work." Human Services Group distributes back to work centers any surpluses that are not reinvested in accordance with the profitability of their merchandise. This should allow participating centers to enlarge their productive capacity by increasing the funds available to them for hiring more disabled workers, increasing the hours of those already employed at the WAC, or purchasing additional equipment.

The grantee organization targets the market for each product or line of products, identifies journals and magazines that best reach that target population, and tests its advertisements in those periodicals. Testing allows measurement of the response rates from the advertisements and the WAC's capacity to meet the demand that is generated, and establishment of competitive prices. Full-scale marketing of products is initiated by placing direct response advertisements in established journals and magazines.

INDEX--AWARDEE ORGANIZATIONS

INDEX--AWARDEE ORGANIZATIONS

The Abel Company, 156
Action Management Corporation, 246
Acton Associates, 103
Allergy and Asthma Consultants, 157
Alpha Group Systems, 129
American Innovation, Inc., 47, 212, 233
American Science and Engineering, Inc., 95
Amitec, 211
AMRON Management Consultants, Inc., 48
Anaerobe Systems, 8
Anatole J. Sipin Company, Inc., 49, 158, 159
Antibodies Incorporated, 50
Applied Biomedical Corporation, 51, 116
Applied Research Associates, Inc., 52
Aquatic Terrestrial Research (ATR) Corporation, 121
Arzco Medical Electronics, Inc., 160
Ash Medical Systems, Inc., 28
ASIP, Inc., 230
Associated Enterprise Development, Inc., 254
Athena Group Data Systems, 104
Athtec Systems, 29
Atlantic Antibodies, 9
Atlantic Resources Corporation, 247
Audiological Engineering Corporation, 207
Automated Diagnostic Systems, Inc., 161

Babeco, 112
Bak Electronics, Inc., 198
Beech Hill Enterprises, Inc., 1
Behavioral Health Systems, 162
Bend Research, Inc., 53
Berkeley Planning Associates, 240, 242, 243
Biofusion-RMD, 54
Biomagnetic Technologies, Inc., 42, 163, 208
Biomedical Literature Intelligence Services, 223
Biomedical Research Lab, Inc., 96
Biomedics, Inc., 43, 105, 164, 191
Bio-Metric Systems, Inc., 122, 165, 228
Bionique Laboratories, Inc., 128
Bioqual, Inc., 113
Biostatistical Services, Inc., 55
Biosyne Corporation, 56
Biotech Research Laboratories, Inc., 166
Biotek, Inc., 106
Bonneville Scientific, 167
BRinc, 10

Candela Corporation, 44, 130
Cape Cod Research, Inc., 224
Catheter Research, Inc., 168
Cell Analysis Systems, Inc., 96, 192

Center for Preventive Therapy and Rehabilitation, Inc., 248
Center for Reptile & Amphibian Propagation, Inc., 213
Cerebral Monitoring Systems, 199
Charles Evans & Associates, 150
Chiron Corporation, 151
Clyde Computing Service, 231
Codon, 27
Collaborative Research, Inc., 57
Computer Consulting and Programming Associates, 255
Control Dynamics Company, 169
Cortech, Inc., 170
Covalent Associates, Inc., 200
CST, Inc., 58
Cytogen Research and Development, Inc., 114
CytoTech International, Inc., 56

Daniel Kerschensteiner and Associates, 30
Data Sciences, 45
Delta Metals, Inc., 11
Delta Systems, 123
Denver Biomaterials, Inc., 171
Deseret Research Company, 172
Device Labs, Inc., 97
Digital Analysis Corporation, 2
Digital Scintigraphics, Inc., 123
DNAStar, 152
Dymax Corporation, 59

Ecosystems, Inc., 136
Electronic Design & Research, Inc., 173
Emerson & Stern Associates, 201
Energy Materials Research Company, 129
Enzo Biochem, Inc., 12, 137
ESA, Inc., 214

Fitness Information Technology, 3
Foster-Miller, Inc., 120
Four J and Associates, 249

Gene Labs, Inc., 12, 13, 138
Genetic Diagnostics Corporation, 14, 15, 227
Genetic Systems Corporation, 16
Genzyme Corporation, 31
Geomed, Inc., 32
Gibson-Hunt Associates, Ltd., 250
Giner, Inc., 33, 173, 198
Glass and Ceramics International, Inc., 34
Great Lakes BioScience, 17
Guild Associates, Inc., 35
Gumbs Associates, Inc., 117

Harrick Scientific Corporation, 139
Hawaii Biotechnology Group, Inc., 27
HCR, 245

HealthCare Affiliates, Inc., 174
Health Designs, Inc., 60
HemaScience Laboratories, Inc., 175
Here, Inc., 215
HGPARS Pharmaceutical Laboratories, Inc., 61, 153
Hoover Keith & Bruce Inc., 239
Human Services Group, Inc. 257
Hybridoma Sciences, Inc. 31, 62, 63, 64, 176

ICS Medical Corporation, 209
Illiana Aviation Science, 131
Immunogenics Corporation, 66
ImmunoMed Corporation, 18
Immuno Modulators Laboratories, Inc., 65
IMRE Corporation, 67, 68
Industrial & Biomedical Sensors Corporation, 193
INET Corporation, 177
Innovative Technology, Inc., 124
Integrated Genetics, Inc., 194
International Micro Images, 140
International Resource Development, Inc., 232
Intron, Inc., 125
Ionomet Corporation, 216
IOX Assessment Associates, 195
Isotechnologies, Inc., 154

JCL Clinical Research Corporation, 69, 70
Jonas, Inc., 4
JWK International Corporation, 36

K & C Medical, 71
Keneko Communications, Inc., 107, 244
Kermath Manufacturing Corporation, 234
KMS Fusion, Inc., 98, 139, 141
Kron Research and Consulting Corporation, 46

Laboratory Sciences Institute, Ltd., 142
Lawrence Medical Systems, 196
Lawton Scientific, Inc., 19
Levine Associates, Inc., 221
Loats Associates, Inc., 72
Lohocla Corporation, 225
LVAD Technology, Inc., 178

Macy Research Associates, 109
Maret Consulting Services, 179
Marshall Long/Acoustics, Inc., 202
McCormick Laboratories, Inc., 180
Med Data Associates, Inc., 236
Medical Instrument Development Laboratories, Inc., 37
MEDPACIFIC Corporation, 118
M.L. Meeks Associates, 108
Membrane Technology and Research, Inc., 119
Meridian Instruments, Inc., 73

Merix Corporation, 74
Migatron Corporation, 4
Moco, Inc., 235
Molecular Biosystems, Inc., 20, 21, 75, 76
Molecular Diagnostics, Inc., 22
Moleculon Research Corporation, 181

Neogen Corporation, 77
Neuro Logic Systems, 132
Neurometrix, 203
North Valley Farms, Inc., 38
North West Labs, Inc., 23
Northwestern Aquatic Sciences, Inc., 126
Nova Pharmaceutical Corporation, 204
NuTech Industries, Inc., 182

Optical Technologies, Inc., 183
OPTRA, Inc., 124, 127, 143
Optron Systems, Inc., 78
ORD, Inc., 24, 217
Orphan Designed Drugs, Inc., 24

Pathfinder Enterprises, 197
P.C. Inc., 79
Peptide Analysis Laboratory, 80
Phospho-Energetics, Inc., 108
PhotoMetrics, Inc., 81
Plasma Tech Corporation, 133
Polysciences, Inc., 138, 144
Prototypes, Inc., 226
Psytech, Inc., 184

Q-T Products, Inc., 134
Quantatec International, Inc., 99
Quantitative Medical Systems, Inc., 82
Quantitative Services, Inc., 251

Radiation Associates, Inc., 83
Radiation Monitoring Devices, Inc., 145, 146, 185, 222
Ratel-Medical Imaging Labs, 84
RCI, 229
Recomtex Corporation, 25
Respitrace Corporation, 110
Rimstar Systems, 99, 135
Rogers and Associates Engineering Corporation, 85

Scanicon Corporation, 86
SCI Development Corporation, 186
Scientific Systems, Inc., 187
Scott Instruments Corporation, 205
Senior Software, Inc., 5

Sociometrics Corporation, 241
Sodal & Bowman Company, 188
Southern Sandoval Investments, Ltd., 252
Spiral System Instruments, Inc., 26
Spire Corporation, 39
Statistics and Epidemiology Research Corporation, 87
Sterilization Technical Services, Inc., 88
Summa Medical Corporation, 89, 100
Sunol Sciences Corporation, 218
Suprex Corporation, 147
Sweet Dreems, Inc., 115
SynChrom, Inc., 148

Tacticon Corporation, 7
Talcott Development, Inc., 206
Technical Programming Services, 90
Technical Research Associates, Inc., 46, 189, 197
Technical Resources, Inc., 91
Telefactor Corporation, 210
Tobitron, Inc., 219
Toconis & Associates, Personnel Service, 253
Tone Brothers, Inc., 238
Tracer Technologies, Inc., 40, 101, 111, 190
Triangle Research and Development Corporation, 6, 102
Tripos Associates, Inc., 149

Urban Systems Research and Engineering, Inc., 256

Ventec Laboratories, Inc., 37
Vestar Research, Inc., 92, 93, 94
Vestec Corporation, 155
Verité Technology Group, 90
Viking Instruments Corporation, 83
Viscotek Corporation, 149
Vitalog Corporation, 41

Western Research Company, 146

Yoder, Inc., 237

Zofcom Assistives, 220

INDEX--STATE/AWARDEE ORGANIZATION

INDEX--STATE/AWARDEE ORGANIZATION

Alabama
- Amitec, 211
- Control Dynamics Company, 169
- Four J and Associates, 249

Arizona
- Rimstar Systems, 99, 135
- Western Research Company, 146

California
- Alpha Group Systems, 129
- Anaerobe Systems, 8
- Antibodies Incorporated, 50
- Aquatic Terrestrial Research (ATR) Corporation, 121
- Athtec Systems, 29
- Berkeley Planning Associates, 240, 242, 243
- Biomagnetic Technologies, Inc., 42, 163, 208
- Center for Reptile & Amphibian Propagation, Inc., 213
- Charles Evans & Associates, 150
- Chiron Corporation, 151
- Codon, 27
- Emerson & Stern Associates, 201
- Energy Materials Research Company, 129
- Gene Labs, Inc., 12, 13, 138
- Glass and Ceramics International, Inc., 34
- HealthCare Affiliates, Inc., 174
- HemaScience Laboratories, Inc., 175
- Here, Inc., 215
- INET Corporation, 177
- IOX Assessment Associates, 195
- Keneko Communications, Inc., 107, 244
- Maret Consulting Services, 179
- Marshall Long/Acoustics, Inc., 202
- Medical Instrument Development Laboratories, Inc., 37
- Membrane Technology and Research, Inc., 119
- Molecular Biosystems, Inc., 20, 21, 75, 76
- Neuro Logic Systems, 132
- Quantatec International, Inc., 99
- Quantitative Medical Systems, Inc., 82
- Ratel-Medical Imaging Labs, 84
- Scanicon Corporation, 86
- Senior Software, Inc., 5
- Sociometrics Corporation, 241
- Sunol Sciences Corporation, 218
- Tacticon Corporation, 7
- Talcott Development, Inc., 206
- Technical Programming Services, 90
- Toconis & Associates, Personnel Service, 253
- Verité Technology Group, 90
- Vestar Research, Inc., 92, 93, 94
- Vitalog Corporation, 41
- Zofcom Assistives, 220

Colorado
Cortech, Inc., 170
Denver Biomaterials, Inc., 171
Quantitative Services, Inc., 251
Sodal & Bowman Company, 188

Connecticut
ASIP, Inc., 230
Lawton Scientific, Inc., 19

Delaware
Jonas, Inc., 4

District of Columbia
Athena Group Data Systems, 104
Gibson-Hunt Associates, Ltd., 250
HCR, 245
Urban Systems Research and Engineering, Inc., 256

Florida
Clyde Computing Service, 231
ImmunoMed Corporation, 18
Pathfinder Enterprises, 197

Georgia
Hybridoma Sciences, Inc., 31, 62, 63, 64, 176

Hawaii
Hawaii Biotechnology Group, Inc., 27

Idaho
North West Labs, Inc., 23

Illinois
Acton Associates, 103
Arzco Medical Electronics, Inc., 160
Cell Analysis Systems, Inc., 96, 192
ICS Medical Corporation, 209
International Resource Development, Inc., 232
Lohocla Corporation, 225
Migatron Corporation, 4
Plasma Tech Corporation, 133

Indiana
Ash Medical Systems, Inc., 28
Catheter Research, Inc., 168
SynChrom, Inc., 148
Tone Brothers, Inc., 238
Yoder, Inc., 237

Kansas
International Micro Images, 140

Kentucky
Electronic Design & Research, Inc., 173

Louisiana
CST, Inc., 58

Maine
Atlantic Antibodies, 9
Beech Hill Enterprises, Inc., 1
Computer Consulting and Programming Associates, 255

Maryland
Associated Enterprise Development, Inc., 254
Bak Electronics, Inc., 198
Bioqual, Inc., 113
Biotech Research Laboratories, Inc., 166
BRinc, 10
Center for Preventive Therapy and Rehabilitation, Inc., 248
Levine Associates, Inc., 221
Loats Associates, Inc., 72
Nova Pharmaceutical Corporation, 204
P.C. Inc., 79
Peptide Analysis Laboratory, 80
Prototypes, Inc., 226
Spiral System Instruments, Inc., 26
Technical Resources, Inc., 91

Massachusetts
American Science and Engineering, Inc., 95
Applied Biomedical Corporation, 51, 116
Audiological Engineering Corporation, 207
Biofusion-RMD, 54
Biotek, Inc., 106
Candela Corporation, 44, 130
Cape Cod Research, Inc., 224
Cerebral Monitoring Systems, 199
Collaborative Research, Inc., 57
Covalent Associates, Inc., 200
Cytogen Research and Development, Inc., 114
Device Labs, Inc., 97
Digital Scintigraphics, Inc., 123
ESA, Inc., 214
Foster-Miller, Inc., 120
Genzyme Corporation, 31
Giner, Inc., 33, 173, 198
HGPARS Pharmaceutical Laboratories, Inc., 61, 153
Human Services Group, Inc., 257
Industrial & Biomedical Sensors Corporation, 193
Integrated Genetics, Inc., 194
Ionomet Corporation, 216
McCormick Laboratories, Inc., 180
Merix Corporation, 74
M.L. Meeks Associates, 108
Moco, Inc., 235

Massachusetts (continued)
Moleculon Research Corporation, 181
North Valley Farms, Inc., 38
OPTRA, Inc., 124, 127, 143
Optron Systems, Inc., 78
ORD, Inc., 24, 217
PhotoMetrics, Inc., 80
Radiation Monitoring Devices, Inc., 145, 146, 185, 222
Scientific Systems, Inc., 187
Spire Corporation, 39
Tracer Technologies, Inc., 40, 101, 111, 190

Michigan
Action Management Corporation, 246
Delta Metals, Inc., 11
Great Lakes BioScience, 17
KMS Fusion, Inc., 98, 139, 141
LVAD Technology, Inc., 178
Meridian Instruments, Inc., 73
Neogen Corporation, 77
Recomtex Corporation, 25
Ventec Laboratories, Inc., 37

Minnesota
Bio-Metric Systems, Inc., 122, 165, 228
Data Sciences, 45
Laboratory Sciences Institute, Ltd., 142

Mississippi
Innovative Technology, Inc., 124

Missouri
Biomedical Research Lab, Inc., 96
Tripos Associates, Inc., 149

Nebraska
Delta Systems, 123

New Hampshire
Tobitron, Inc., 219

New Jersey
Biostatistical Services, Inc., 55
CytoTech International Inc., 56
Daniel Kerschensteiner and Associates, 30
Geomed, Inc., 32
Gumbs Associates, Inc., 117
Orphan Designed Drugs, Inc., 24

New Mexico
Applied Research Associates, Inc., 52
Illiana Aviation Science, 131
Southern Sandoval Investments, Ltd., 252
Summa Medical Corporation, 89, 100

New York
AMRON Management Consultants, Inc., 48
Anatole J. Sipin Company, Inc., 49, 158, 159
Behavioral Health Systems, 162
Bionique Laboratories, Inc., 128
Enzo Biochem, Inc., 12, 137
Genetic Diagnostics Corporation, 14, 15, 227
Harrick Scientific Corporation, 139
Health Designs, Inc., 60
Q-T Products, Inc., 134
Respitrace Corporation, 110
Sterilization Technical Services, Inc., 88

North Carolina
American Innovation, Inc., 47, 212, 233
Isotechnologies, Inc., 154
Kron Research and Consulting Corporation, 46
SCI Development Corporation, 186
Triangle Research and Development Corporation, 6, 102

Ohio
Allergy and Asthma Consultants, 157
Guild Associates, Inc., 35
Molecular Diagnostics, Inc., 22
NuTech Industries, Inc., 182
Sweet Dreems, Inc., 115

Oregon
Bend Research, Inc., 53
Biomedical Literature Intelligence Services, 223
Med Data Associates, Inc., 236
Neurometrix, 203
Northwestern Aquatic Sciences, Inc., 126
Psytech, Inc., 184

Pennsylvania
Dymax Corporation, 59
Ecosystems, Inc., 136
K & C Medical, 71
Polysciences, Inc., 138, 144
Suprex Corporation, 147
Telefactor Corporation, 210

South Carolina
Intron, Inc., 125

Tennessee
JCL Clinical Research Corporation, 69, 70

Texas
Biosyne Corporation, 56
Hoover Keith & Bruce Inc., 239
Immuno Modulators Laboratories, Inc., 65
Macy Research Associates, 109
Radiation Associates, Inc., 83
Scott Instruments Corporation, 205
Vestec Corporation, 155
Viscotek Corporation, 149

Utah
Bonneville Scientific, 167
Deseret Research Company, 172
Rogers and Associates Engineering Corporation, 85
Technical Research Associates, Inc., 46, 189, 197

Virginia
The Abel Company, 156
Atlantic Resources Corporation, 247
Automated Diagnostic Systems, Inc., 161
Digital Analysis Corporation, 2
JWK International Corporation, 36
Kermath Manufacturing Corporation, 234
Optical Technologies, Inc., 183
RCI, 229
Viking Instruments Corporation, 83

Washington
Babeco, 112
Biomedics, Inc., 43, 105, 164, 191
Fitness Information Technology, 3
Genetic Systems Corporation, 16
Immunogenics Corporation, 66
IMRE Corporation, 67, 68
Lawrence Medical Systems, 196
MEDPACIFIC Corporation, 118
Statistics and Epidemiology Research Corporation, 87

Wisconsin
DNAStar, 152

*U.S. GOVERNMENT PRINTING OFFICE:1985-478:510

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health
Westwood Bldg., Room 449
Bethesda, Maryland 20205

Official Business
Penalty for Private Use $300

Postage and Fees Paid
U.S. Dept. of HHS
HHS 396

Special Fourth-Class
Rate